"The neonatal Fc receptor (FcRn) – not just for kids!"

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Diesase models

Autoimmunity
Allergy

Technology

Molecular and cellular biology

Multidisiplinary – synergy

Reveal the mechanisms that cause immunological diseases

Development of novel immunoregulatory molecules

Translational research

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The research group of humoral immunity and homeostasis

The Research Council of Norway

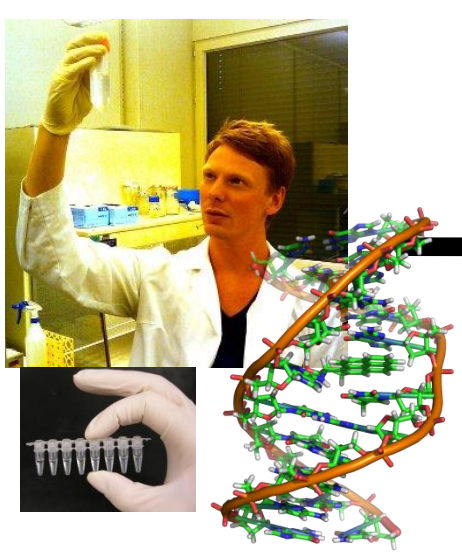
Oslo University Hospital

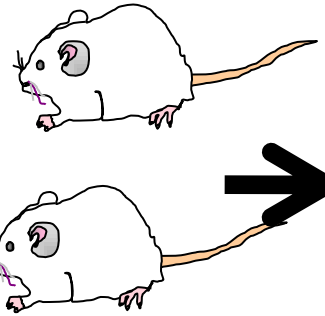
http://www.med.uio.no/cir

Aims

- **Understand the importance of the neonatal Fc receptor (FcRn) on biology/immunology.**

- **Understand how FcRn functions can be theraputically utilized.**

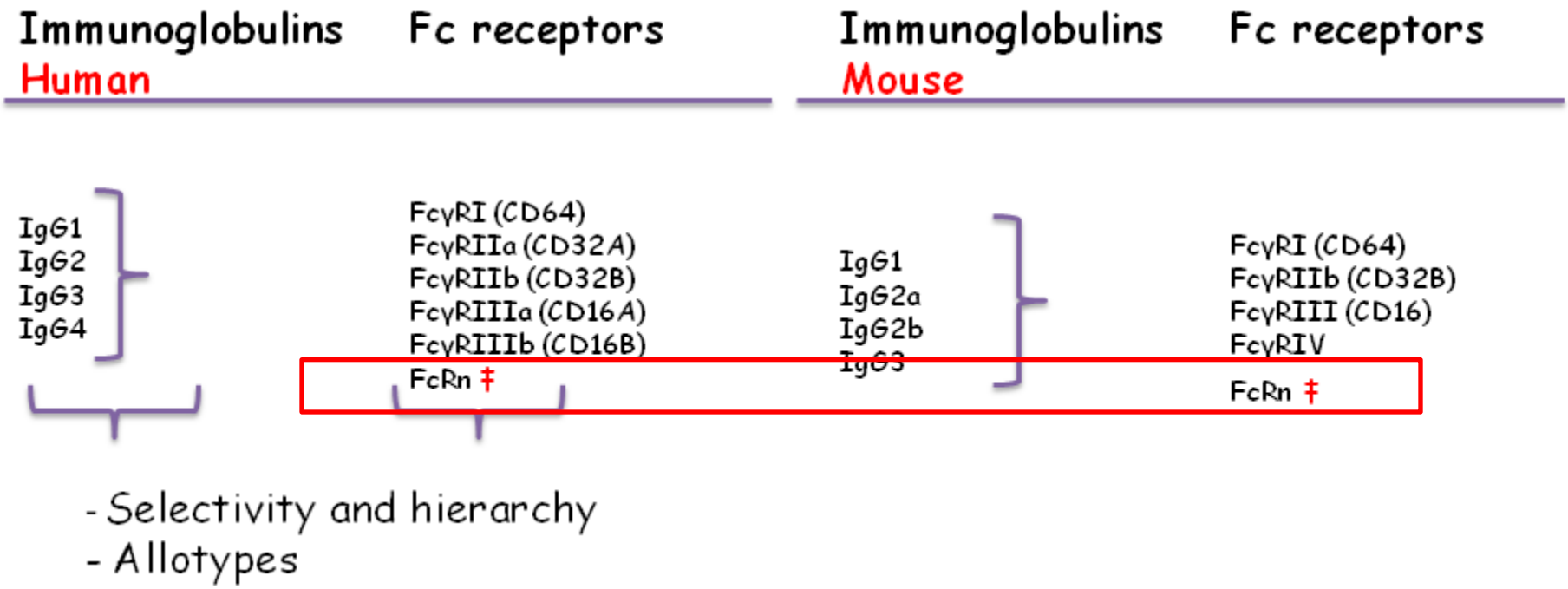




Basic **Preclinical** **Manufacturing** **Treatment of disease**

- **Understanding how basic biology can be translated into therapy.**

The diversity of IgGs and Fcγ receptors:



- **FcRn is a non-classical FcγR, MHC class I-related.**
- **More widely expressed (endotehial and epithelial cells), not restricted to hematopoietic cells.**
- **Predominantly expressed within endosomal compartments.**
- **Binds all 4 IgG subclasses.**

FcRn is a versatile receptor

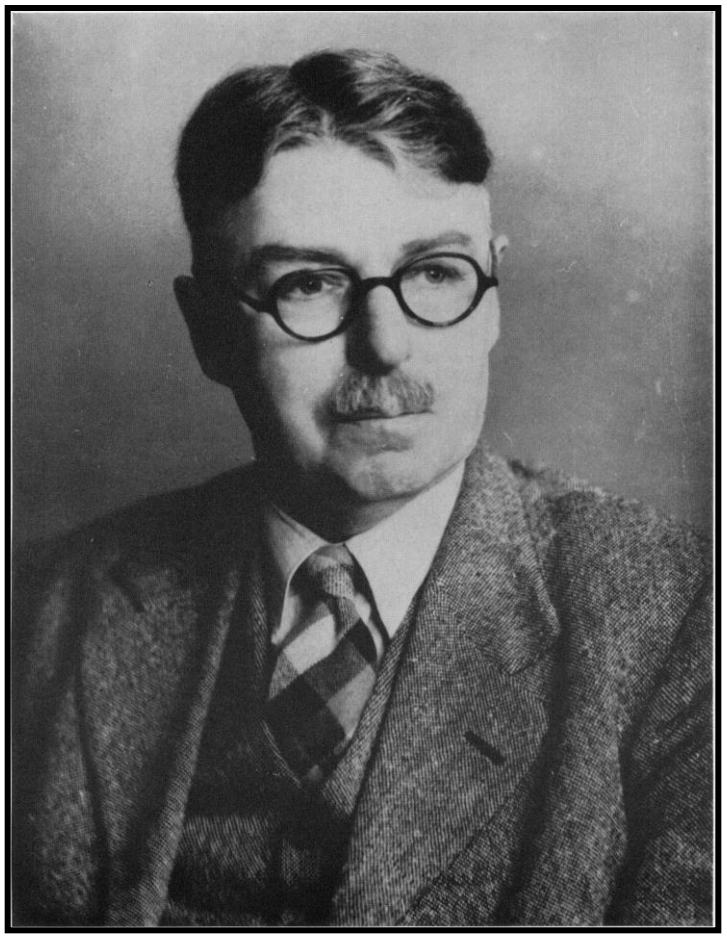
- Transepithelial transport of IgG (intestine; epithelial cells)
- Transepithelial transport of IgG (lung; alveolar epithelial cells)
- Transplacental transport of IgG (placenta; syncytiotrophoblasts)
- Half-life regulation of IgG and albumin (endothelial and hematopoietic cells)
- Kidney clearance of IgG (podocytes)
- Blood brain barrier transport of IgG (endothelium and choroid plexus)
- Antigen presentation of IgG-containing ICs (antigen presenting cells)
- Phagocytosis of IgG-opsonized bacteria (neutrophils)
- Liver, vectorial transport (serum vs bile) of IgG (and albumin) (hepatocytes, sinusoidal cells and Kupffer cells)

FcRn from a historical perspective

FW Rogers Brambell (1901-1970).
- a British fisherman that discovered FcRn

1930-1968: Professor of Zoology, Bangor University in North Wales.
- Established a Department of Marine Biology.

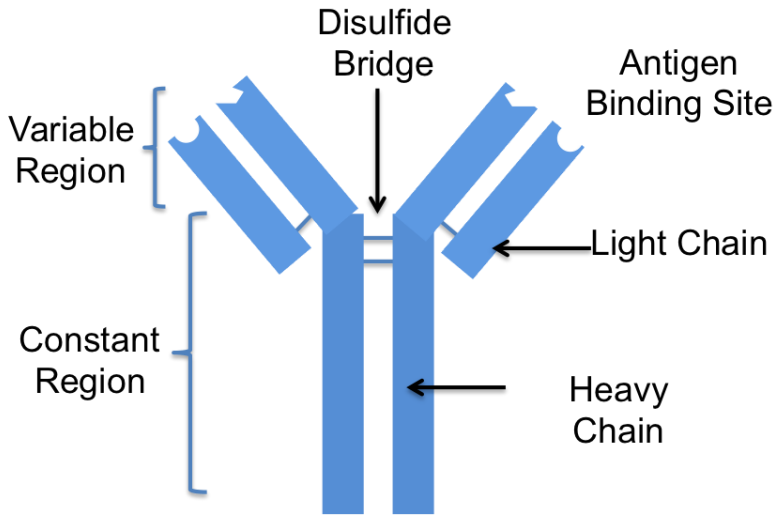
"He was focused on research and was good to work for, but he was a bit detached from this present world. He used to go home at 4 o'clock in order to go fishing in the lake on the Isle of Anglesey".



From fish to rabbits.....

- 2 World War! Atlantic blockade by U-boats, the Government was worried about feeding the people.
- Rabbits were becoming scarce!!
- Of all the most unbelievable assignments, Brambell was given the task of increasing the production rate/fecundity of rabbits.
- He started to examine the cause of rabbit miscarriages, and he studied the transport of substances to the fetus.
- He found the presence of several proteins derived from the rabbit mother's blood in the blood of the fetus.
- Surprisingly large amounts of maternal IgGs were found.

Selective prenatally transmisson of IgG over the yolk sac was dependent on the constant Fc part



Different species, same mechanism:

- Rabbit; pre-birth (yolk-sac).

- Rodents; post-birth transport of maternal IgG (neonatal intestine).

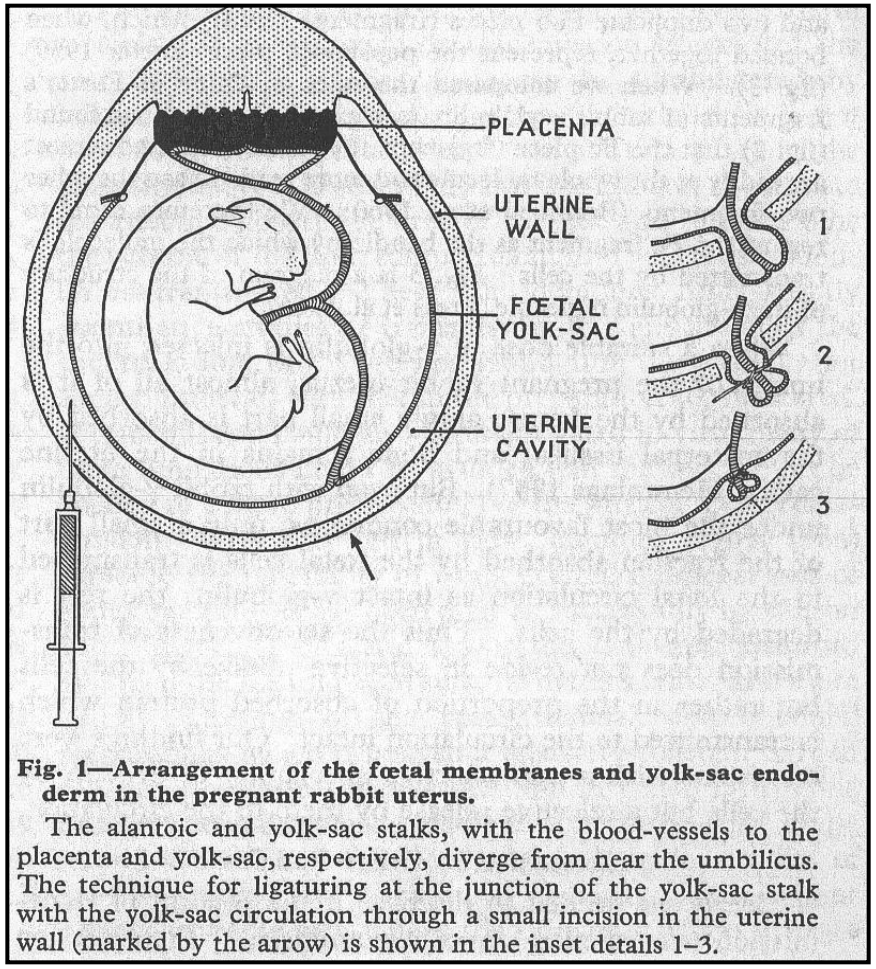


Fig. 1—Arrangement of the fœtal membranes and yolk-sac endoderm in the pregnant rabbit uterus.

The alantoic and yolk-sac stalks, with the blood-vessels to the placenta and yolk-sac, respectively, diverge from near the umbilicus. The technique for ligaturing at the junction of the yolk-sac stalk with the yolk-sac circulation through a small incision in the uterine wall (marked by the arrow) is shown in the inset details 1–3.

The transmission of immunity from mother to young and the catabolism of immunoglobulins. Brambell FW. Lancet. 1966 Nov 19;2(7473):1087-93.

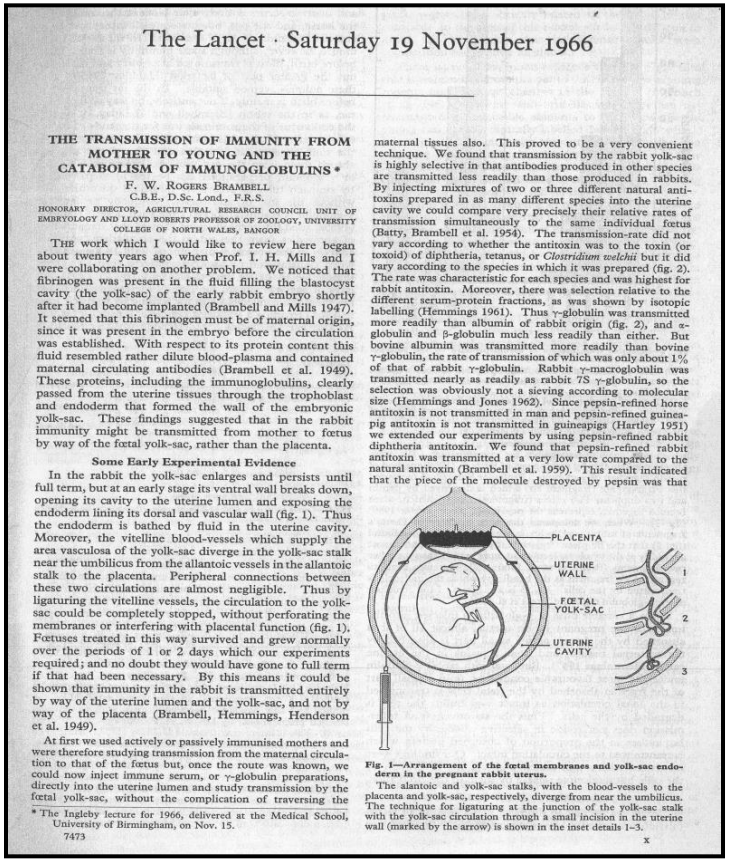
Brambell hypothesis (1966):

"Pinocytosis is well recognized and specific receptors are quite in the most modern fashion…"

"It is suggested that the protein transmitted becomes attached to specific receptors".

"We suggest that attachment to these receptors protects the protein from enzymatic degradation in the cell and that they are located in the walls of the pinocytotic vesicles".

"We believe that it is the Fc part of the H chain which becomes attached to the receptors".



The Lancet · Saturday 19 November 1966

THE TRANSMISSION OF IMMUNITY FROM MOTHER TO YOUNG AND THE CATABOLISM OF IMMUNOGLOBULINS *

F. W. ROGERS BRAMBELL
C.B.E., D.Sc. Lond., F.R.S.

HONORARY DIRECTOR, AGRICULTURAL RESEARCH COUNCIL UNIT OF EMBRYOLOGY AND LLOYD ROBERTS PROFESSOR OF ZOOLOGY, UNIVERSITY COLLEGE OF NORTH WALES, BANGOR

THE work which I would like to review here began about twenty years ago when Prof. I. H. Mills and I were collaborating on another problem. We noticed that fibrinogen was present in the fluid filling the blastocyst cavity (the yolk-sac) of the early rabbit embryo shortly after it had become implanted (Brambell and Mills 1947). It seemed that this fibrinogen must be of maternal origin, since it was present in the embryo before the circulation was established. With respect to its protein content this fluid resembled rather dilute blood-plasma and contained maternal circulating antibodies (Brambell et al. 1949). These proteins, including the immunoglobulins, clearly passed from the uterine tissues through the trophoblast and endoderm that formed the wall of the embryonic yolk-sac. These findings suggested that in the rabbit immunity might be transmitted from mother to fœtus by way of the fœtal yolk-sac, rather than the placenta.

Some Early Experimental Evidence

In the rabbit the yolk-sac enlarges and persists until full term, but at an early stage its ventral wall breaks down, opening its cavity to the uterine lumen and exposing the endoderm lining its dorsal and vascular wall (fig. 1). Thus the endoderm is bathed by fluid in the uterine cavity. Moreover, the vitelline blood-vessels which supply the area vasculosa of the yolk-sac diverge in the yolk-sac stalk near the umbilicus from the allantoic vessels in the allantoic stalk to the placenta. Peripheral connections between these two circulations are almost negligible. Thus by ligaturing the vitelline vessels, the circulation to the yolk-sac could be completely stopped, without perforating the membranes or interfering with placental function (fig. 1). Fœtuses treated in this way survived and grew normally over the periods of 1 or 2 days which our experiments required; and no doubt they would have gone to full term if that had been necessary. By this means it could be shown that immunity in the rabbit is transmitted entirely by way of the uterine lumen and the yolk-sac, and not by way of the placenta (Brambell, Hemmings, Henderson et al. 1949).

At first we used actively or passively immunised mothers and were therefore studying transmission from the maternal circulation to that of the fœtus but, once the route was known, we could now inject immune serum, or γ-globulin preparations, directly into the uterine lumen and study transmission by the fœtal yolk-sac, without the complication of traversing the maternal tissues also. This proved to be a very convenient technique. We found that transmission by the rabbit yolk-sac is highly selective in that antibodies produced in other species are transmitted less readily than those produced in rabbits. By injecting mixtures of two or three different natural antitoxins prepared in as many different species into the uterine cavity we could compare very precisely their relative rates of transmission simultaneously to the same individual fœtus (Batty, Brambell et al. 1954). The transmission-rate did not vary according to whether the antitoxin was to the toxin (or toxoid) of diphtheria, tetanus, or *Clostridium welchii* but it did vary according to the species in which it was prepared (fig. 2). The rate was characteristic for each species and was highest for rabbit antitoxin. Moreover, there was selection relative to the different serum-protein fractions, as was shown by isotopic labelling (Hemmings 1961). Thus γ-globulin was transmitted more readily than albumin of rabbit origin (fig. 2), and α-globulin and β-globulin much less readily than either. But bovine albumin was transmitted more readily than bovine γ-globulin, the rate of transmission of which was only about 1% of that of rabbit γ-globulin. Rabbit γ-macroglobulin was transmitted nearly as readily as rabbit 7S γ-globulin, so the selection was obviously not a sieving according to molecular size (Hemmings and Jones 1962). Since pepsin-refined horse antitoxin is not transmitted in man and pepsin-refined guinea-pig antitoxin is not transmitted in guineapigs (Hartley 1951) we extended our experiments by using pepsin-refined rabbit diphtheria antitoxin. We found that pepsin-refined rabbit antitoxin was transmitted at a very low rate compared to the natural antitoxin (Brambell et al. 1959). This result indicated that the piece of the molecule destroyed by pepsin was that

Fig. 1—Arrangement of the fœtal membranes and yolk-sac endoderm in the pregnant rabbit uterus.

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* The Ingleby lecture for 1966, delivered at the Medical School, University of Birmingham, on Nov. 15.

7473

x

The transmission of immunity from mother to young and the catabolism of immunoglobulins. Brambell FW. Lancet. 1966 Nov 19;2(7473):1087-93.

- So began the research which culminated in the discovery of the Brambell receptor, the so-called neonatal Fc receptor (FcRn)….

The identity of this receptor was finally found and cloned from the intestinal epithelium of neonatal rodents.

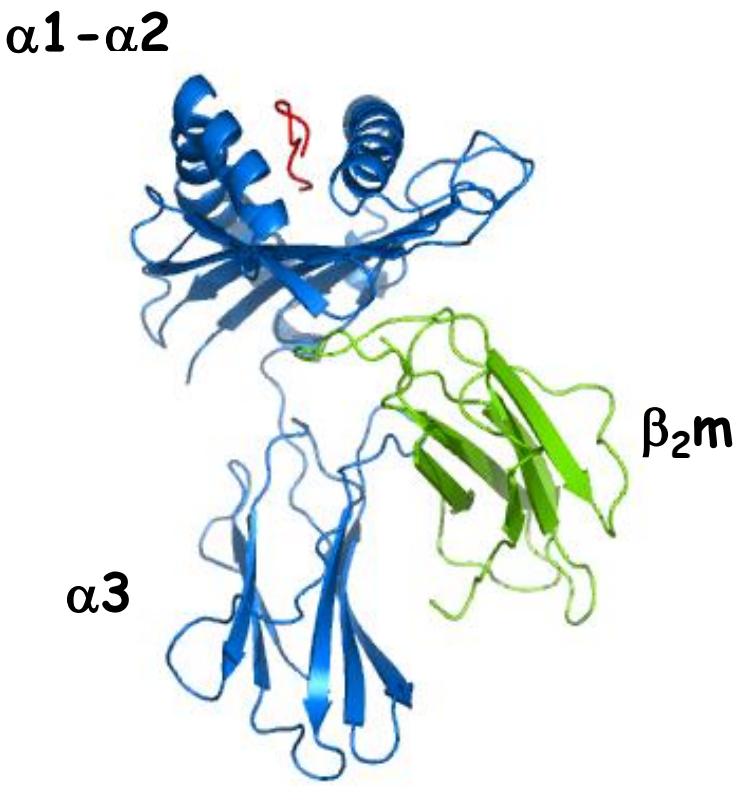
- **An Fc receptor structurally related to MHC class I antigens.**
  Simister, N.E., and Mostov, K.E. (1989). Nature 337, 184-187.

- inspired its name, the neonatal Fc receptor, abrogated FcRn.

- **Crystal structure at 2.2 A resolution of the MHC-related neonatal Fc receptor.**
  Burmeister, W.P., Gastinel, L.N., Simister, N.E., Blum, M.L., and Bjorkman, P.J. (1994). Nature 372, 336-343

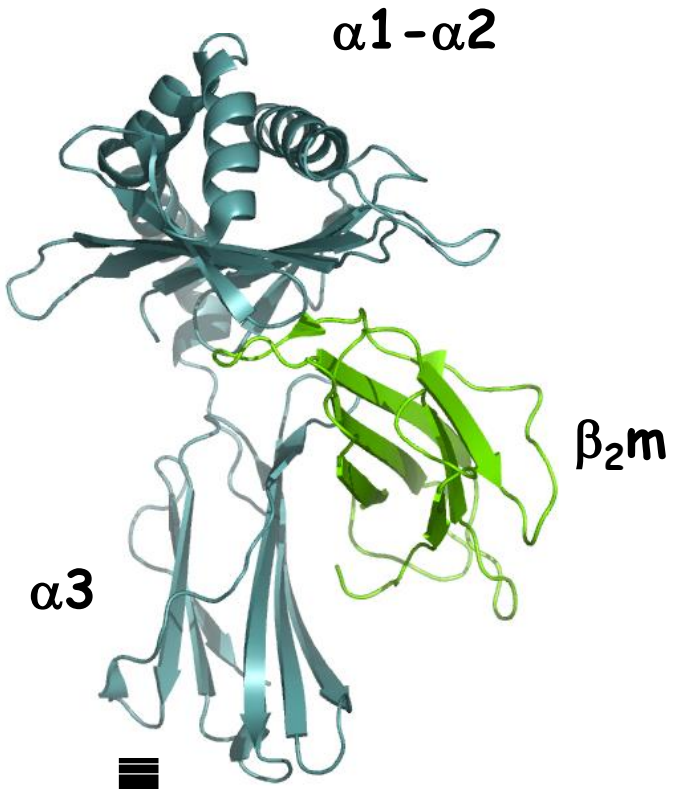
FcRn is a major histocompatibility (MHC) class I-related molecule

MHC class I



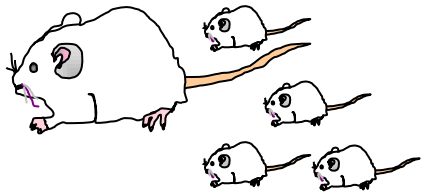
Binds and presents peptides to T-cells

FcRn



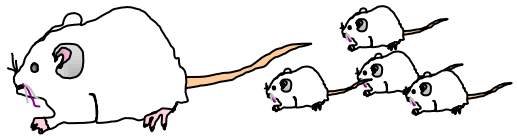
Binds IgG

WT



Transport of IgG
to the neonatal

β2m KO



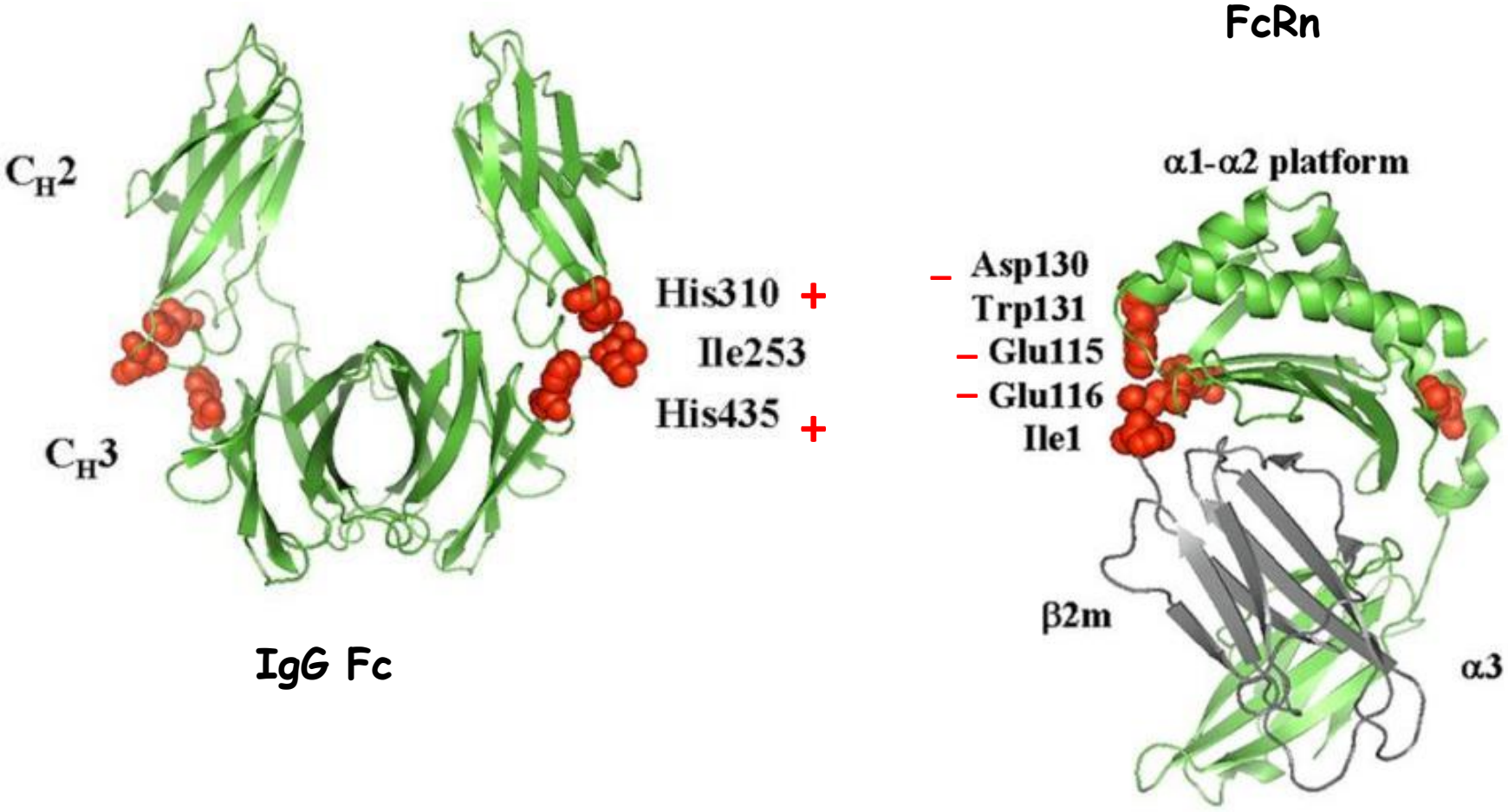
No transport of IgG
to the neonatal

FcRn-mediated transepitelial
delivery of maternal IgG

How is the FcRn specific transport of IgG mediated?

FcRn binds IgG in a strictly pH dependent fashion

pH6.0 pH7.4



Crystal structure of the complex of rat neonatal Fc receptor with Fc. Burmeister, W.P., Huber, A.H., and Bjorkman, P.J. (1994). Nature 372, 379-383.42.

Intestine

pH 6.0

Neonatal rat

- FcRn mediates transepithelial transport of IgG from mother to the neonatal): <u>passive immunization</u>.

Circulation

pH 7.4

A human ortholog?

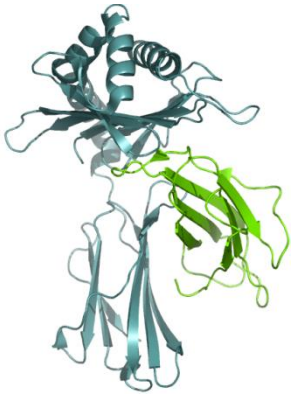
- **A major histocompatibility complex class I-like Fc receptor cloned from human placenta: possible role in transfer of immunoglobulin G from mother to fetus.**

Story CM, Mikulska JE, Simister NE.
J Exp Med. 1994 Dec 1;180(6):2377-81.

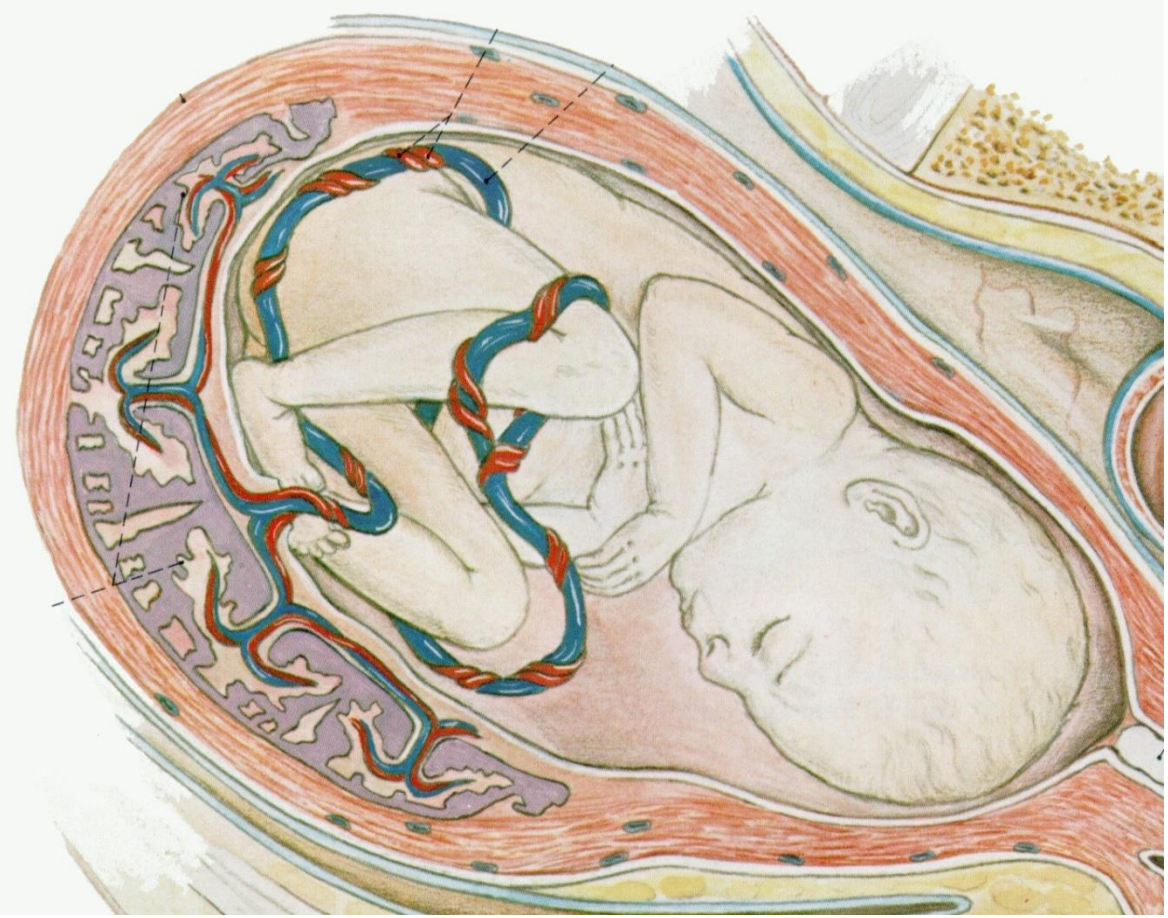
- **Crystal structure and immunoglobulin G binding properties of the human major histocompatibility complex-related Fc receptor.**

West, A.P., Jr., and Bjorkman, P.J. (2000).
Biochemistry *39*, 9698-9708.

- NOT restricted to neonatal rodents.



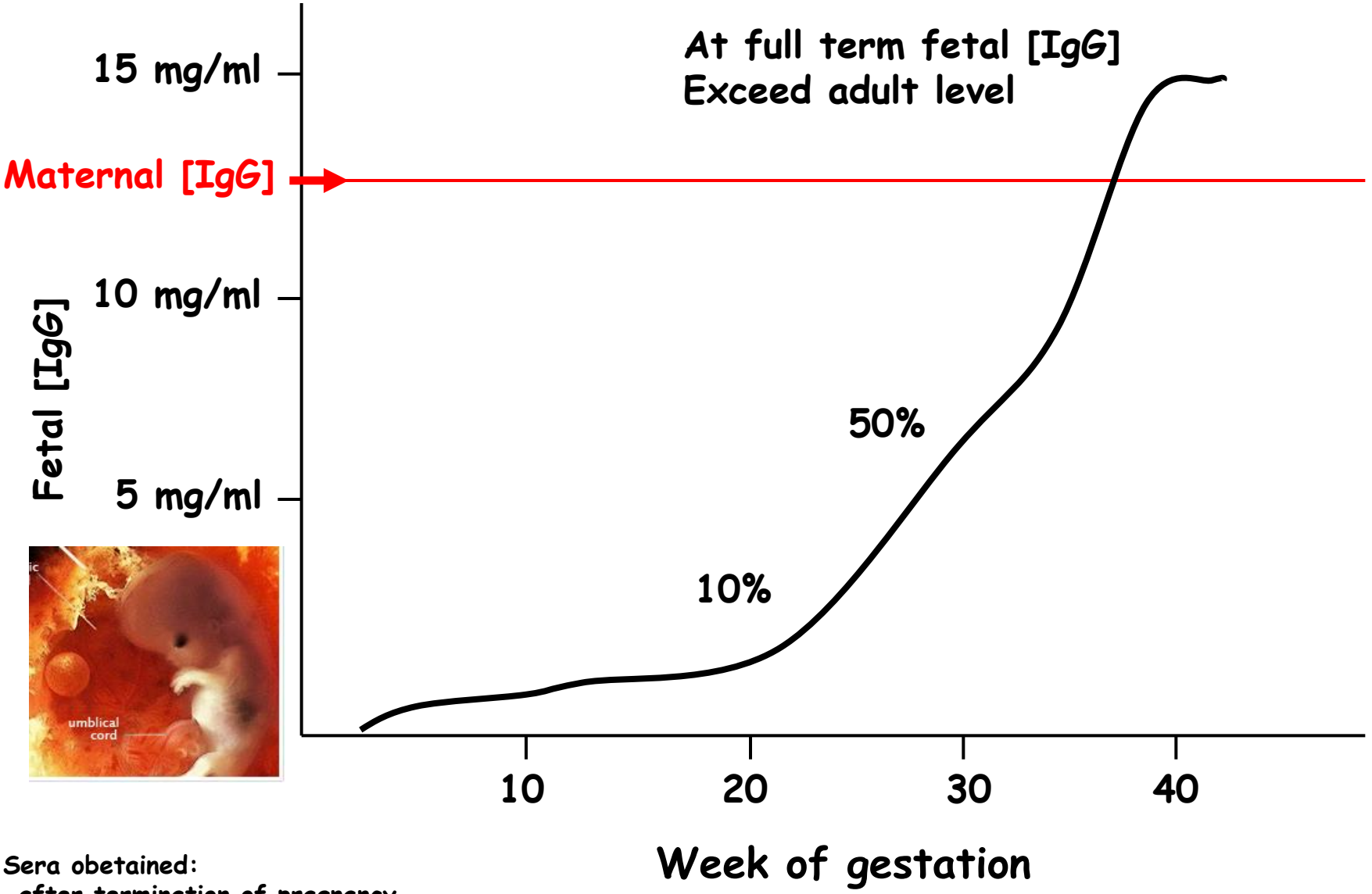
FcRn-mediated transplacental transport of maternal IgG



- **FcRn provides the fetus and newborn with passive humoral immunological protection until the infant starts producing its own IgG**

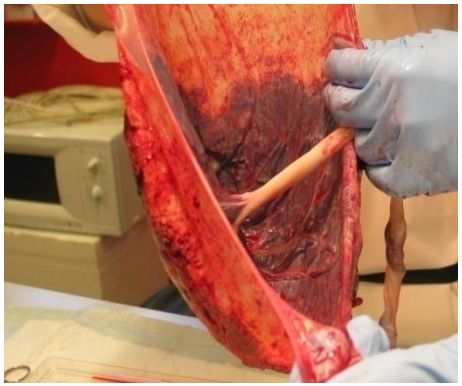
http://pubhealth.ku.dk/placenta/

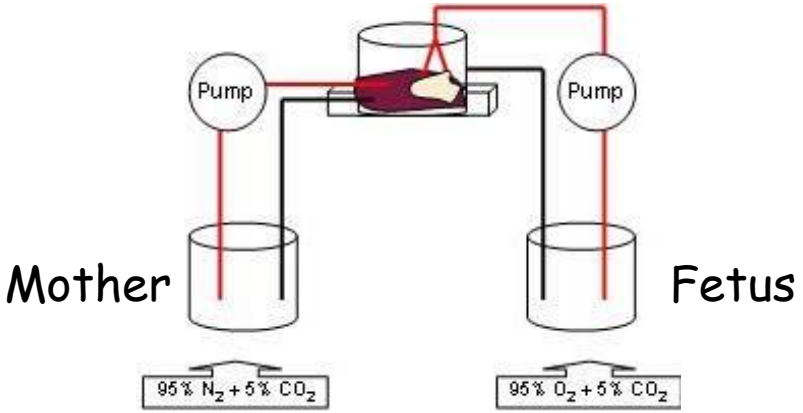
Most IgG in fetal blood is maternal in origin): [IgG] reflects transport from the mother



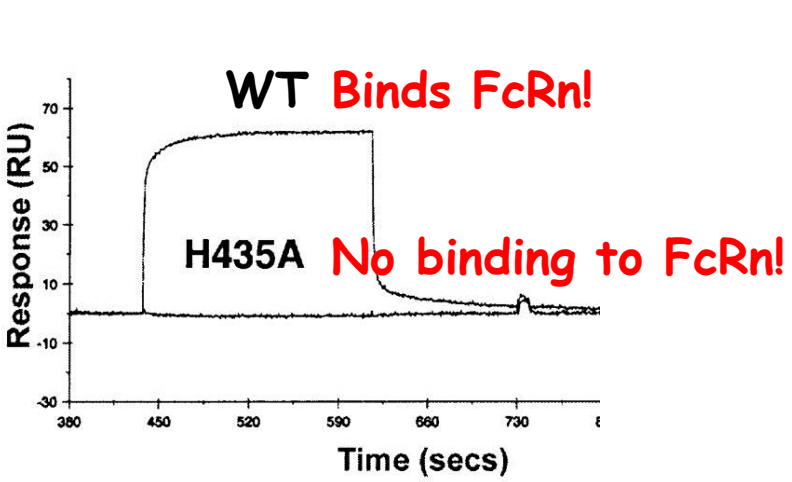
Sera obetained:
-after termination of pragnancy
-from preterm newborns by cordocentesis

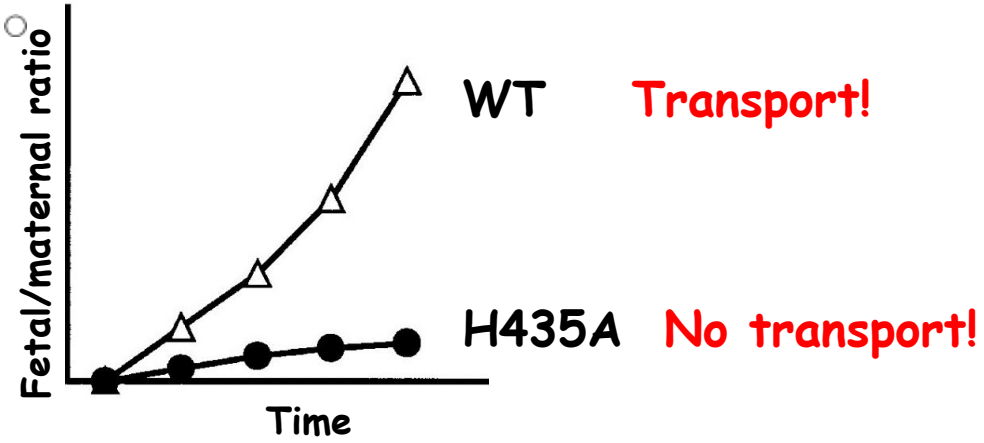
Transport of IgG across placenta is fully dependent on FcRn





Surface plasmon resonance:

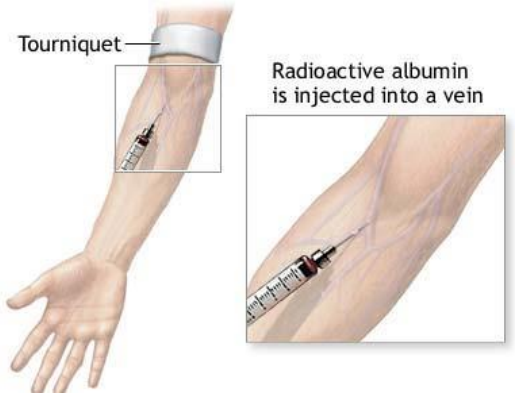




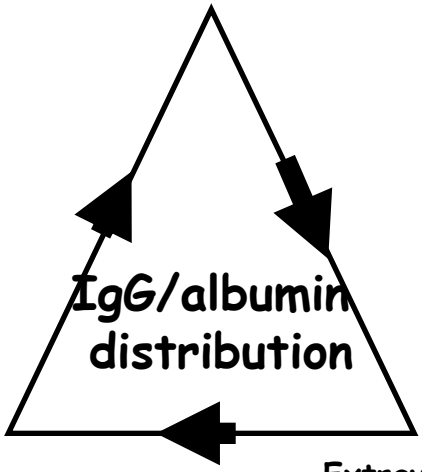
Firan et al. The MHC class I-related receptor, FcRn, plays an essential role in the maternofetal transfer of gamma-globulin in humans. Int Immunol. 2001 Aug;13(8):993-1002.

FcRn is a key regulator of the long half-life of IgG

Biological serum half-life



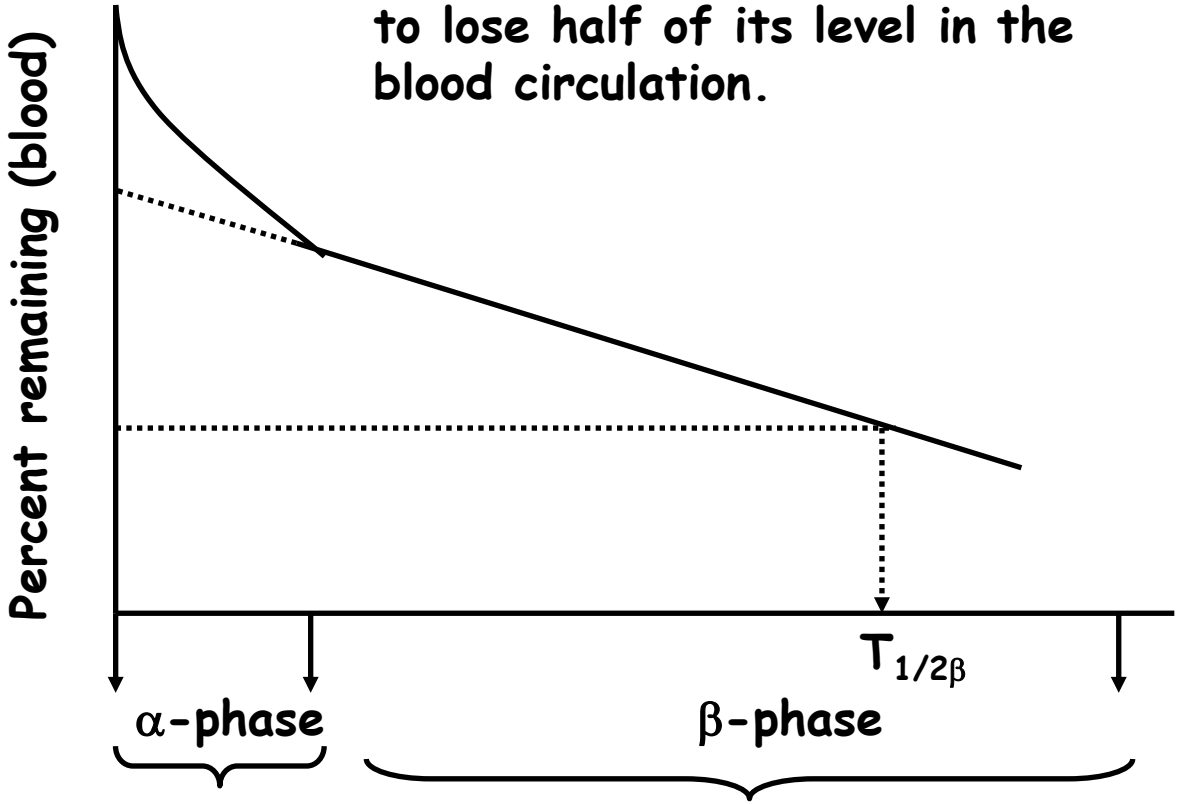
Lymphatic system



Vascular system

Extravascular system

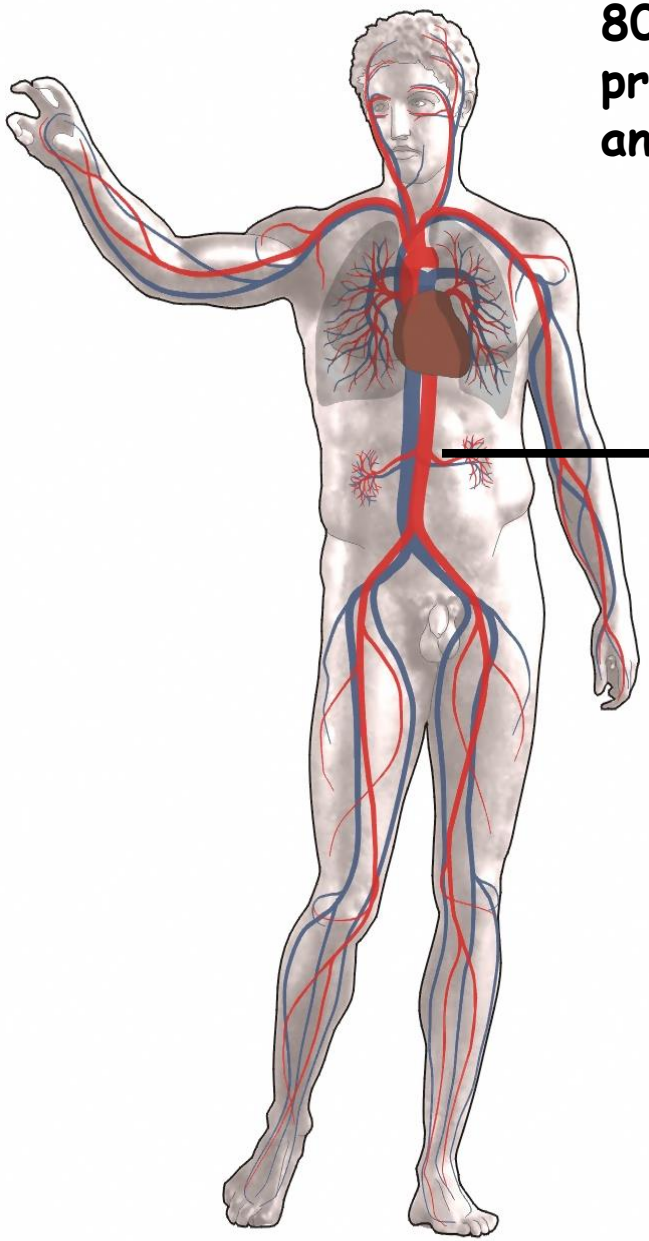
Is the time it takes for a protein to lose half of its level in the blood circulation.



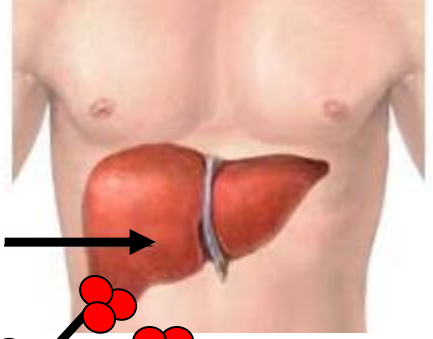
Equilibrium between intra- and extracellular space

Catabolism (biological half-life)

80-90% of the total protein pool in both mouse and man!



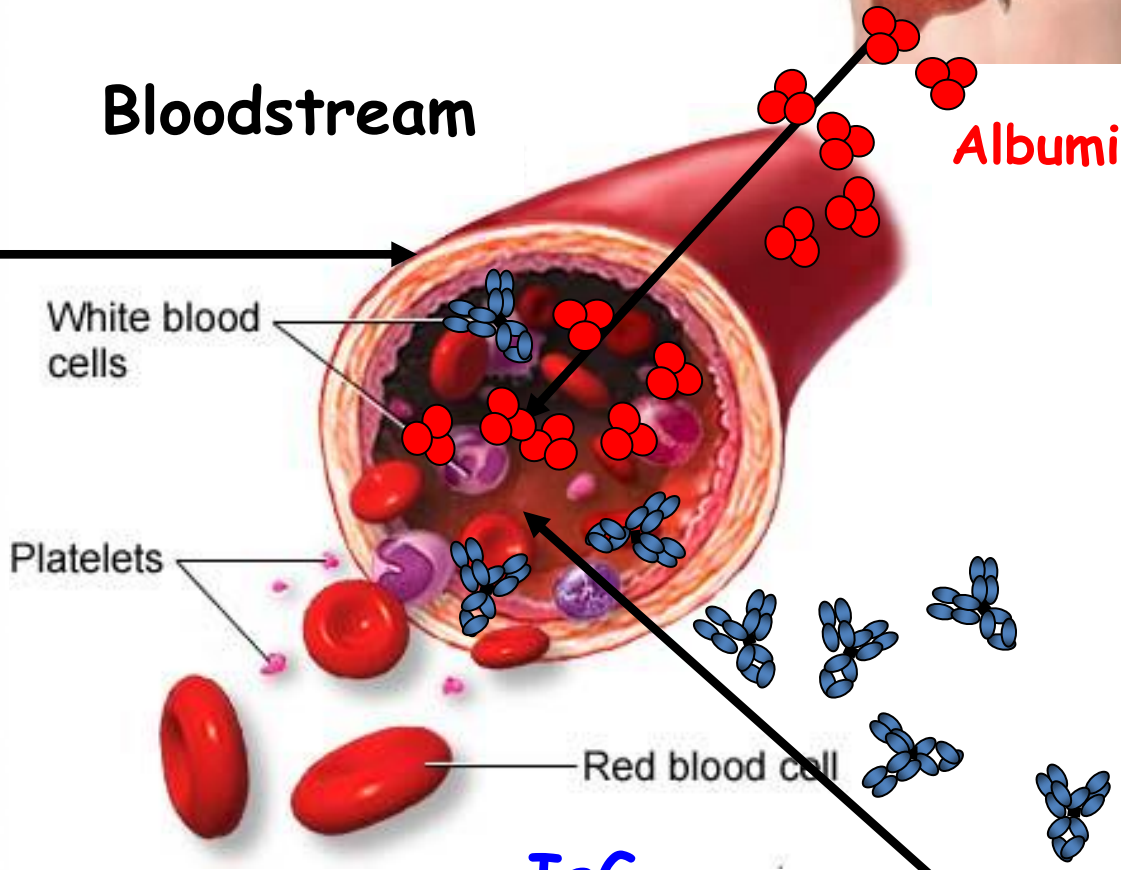
FcRn is globally expressed



Liver

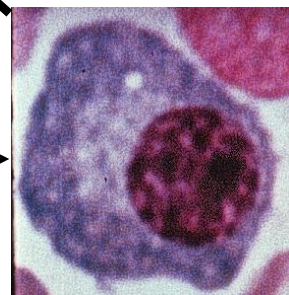
Albumin

Bloodstream

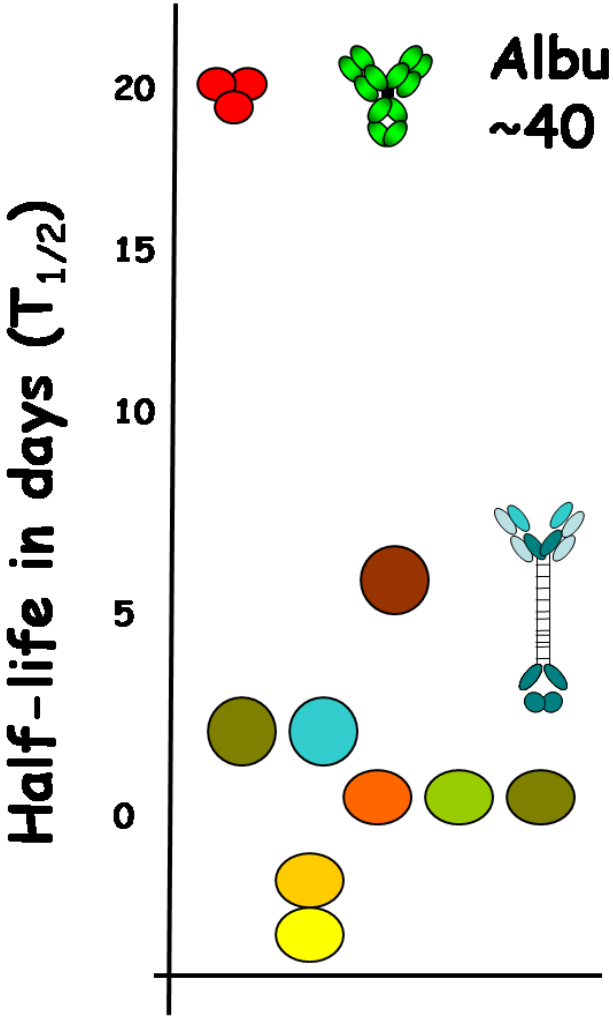


IgG

B/Plasma cells



Different serum proteins have different half-lives



Albumin (~19-20)
~40 mg/ml

IgG1, 2 and 4
(~19-22) ~12 mg/ml

Transferrin (8)

IgG3 (7)

IgM (5) IgA (5)

Lipoprotein (4) Fibrinogen (4) Haptoglobin (4)

IgD (3)

IgE (1)

Why?

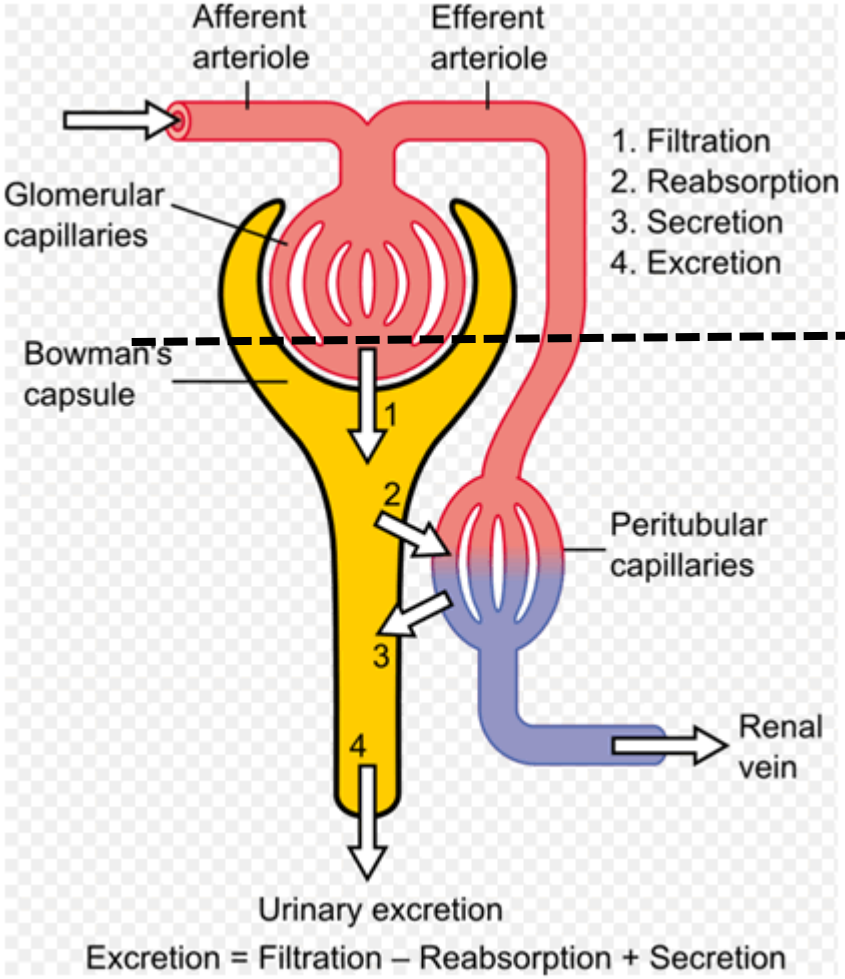
What determines the serum half-life?

- Subseptibility to degradation (proteases).

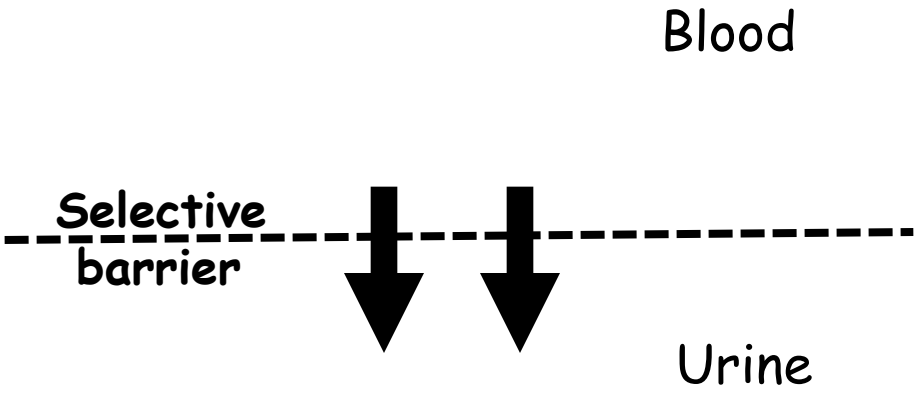
-Molecular weight (MW).

-Binding to other moelcules/cellular receptors (antigen sink effect).

Molecular size and renal clearence threshold



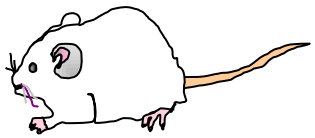
IgG= 150 kDa
Albumin= 67 kDa



The kidneys filtrate 50 plasma volumes daily where waste products end up in the urine.

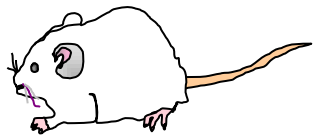
Renal secretion is dependent on the molecular weight; proteins below approx. 60 kDa are excreted while proteins with a size above 60 kDa are retained.

WT



Stable levels of systemic IgG and albumin

FcRn KO



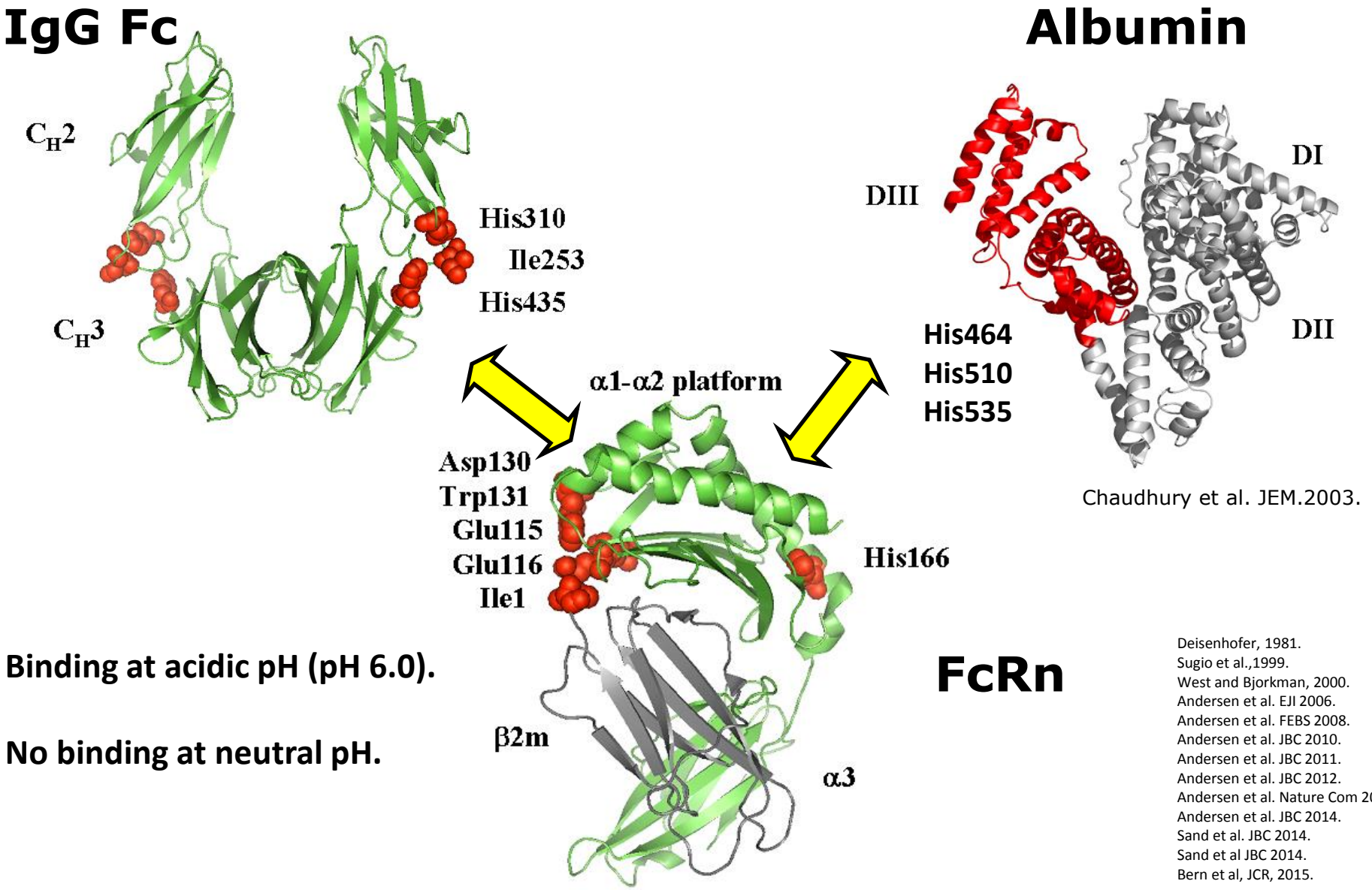
Reduced levels of systemic IgG and albumin

FcRn-mediated homeostatic regulation of IgG and albumin

	WT	Tie2-FcRnflox/flox
IgG1 Half-life:	217h	9h

Roopenian and Akilesh. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007. Conditional deletion of the MHC class I-related receptor FcRn reveals the sites of IgG homeostasis in mice. Montoyo et al. PNAS. 2009.

FcRn binds IgG and albumin in a pH dependent fashion simultaneously

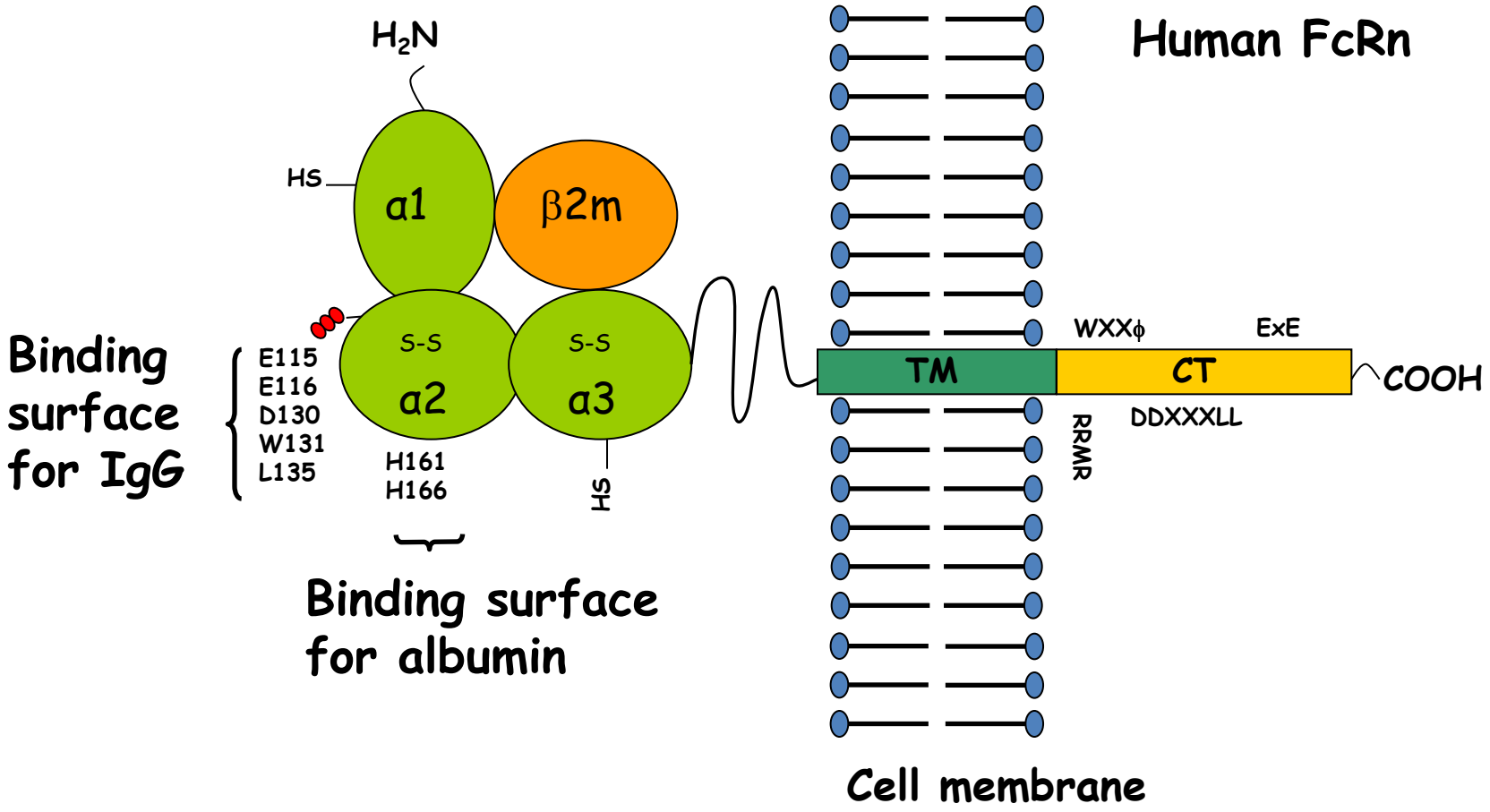


Chaudhury et al. JEM.2003.

- **Binding at acidic pH (pH 6.0).**
- **No binding at neutral pH.**

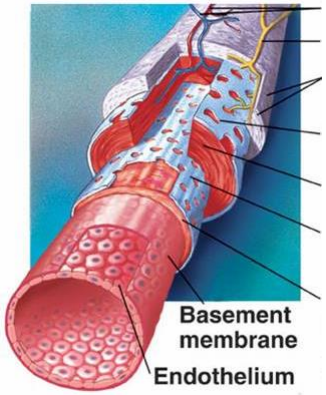
Deisenhofer, 1981.
Sugio et al.,1999.
West and Bjorkman, 2000.
Andersen et al. EJI 2006.
Andersen et al. FEBS 2008.
Andersen et al. JBC 2010.
Andersen et al. JBC 2011.
Andersen et al. JBC 2012.
Andersen et al. Nature Com 2012.
Andersen et al. JBC 2014.
Sand et al. JBC 2014.
Sand et al JBC 2014.
Bern et al, JCR, 2015.

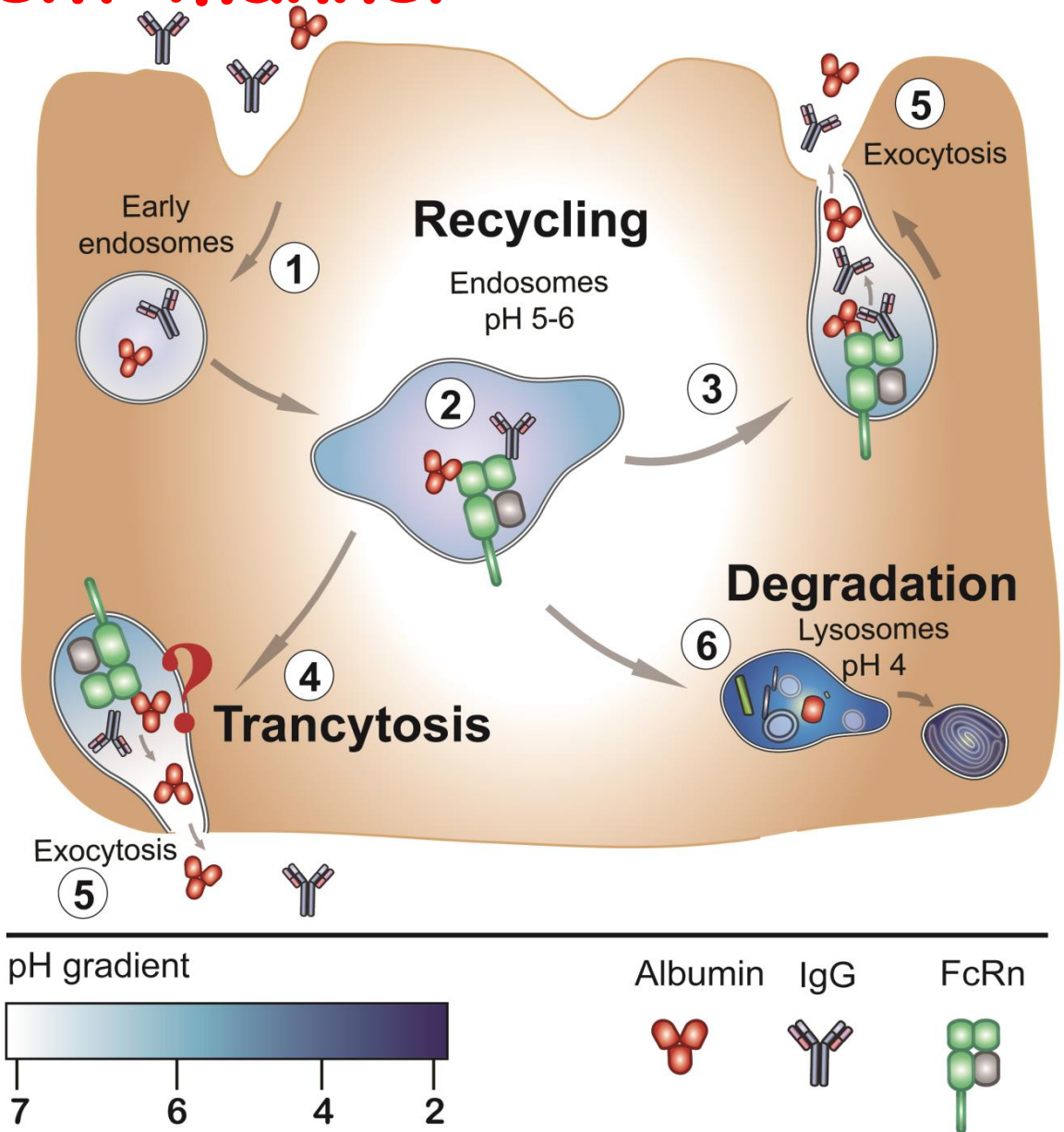
A common receptor, named the neonatal Fc receptor (FcRn), binds IgG and albumin simultaneously



How is FcRn regulating the long half-life of IgG and albumin?

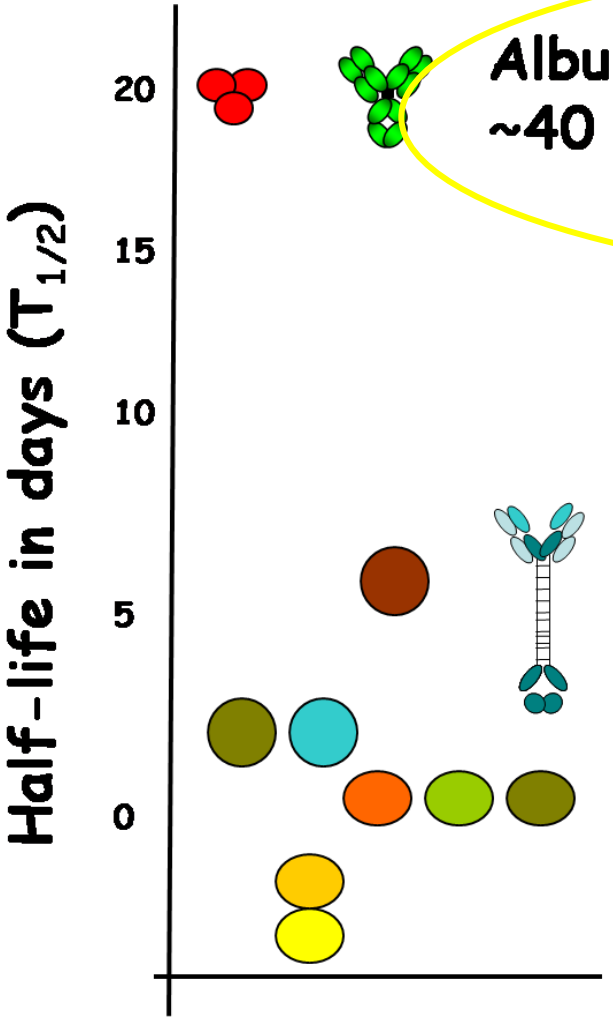
FcRn recycles its ligands in a pH dependent manner





Sand et al, Front Immunol, 2014.

Different serum proteins have different half-lives



Albumin (~19-20) ~40 mg/ml

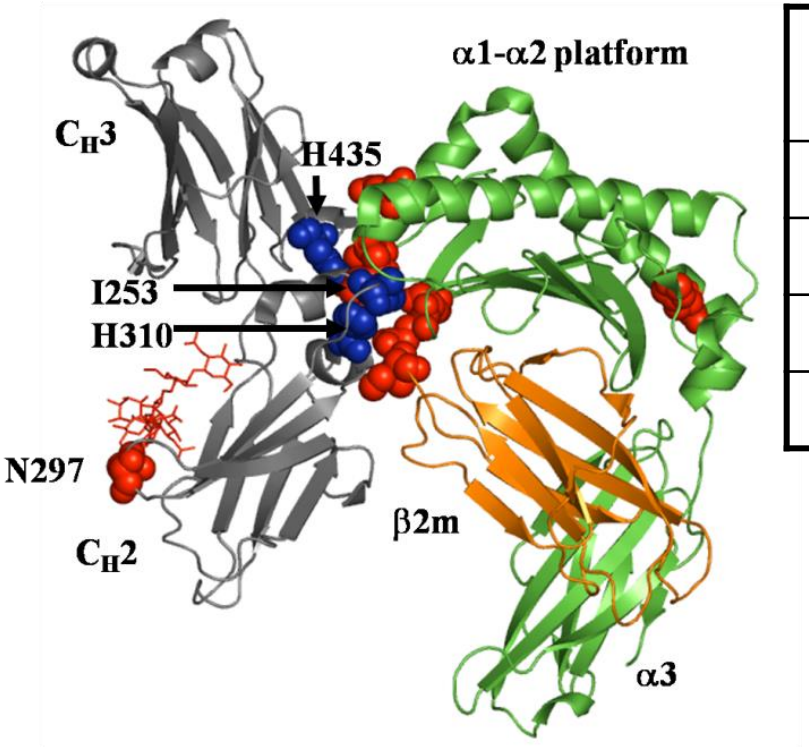
IgG1, 2 and 4 (~19-22) ~12 mg/ml

Why?

- MW above the kidney clearence threshold.
- FcRn mediated recycling.

Modulation of half-life as a function of FcRn binding

- Mutation of amino acid residues in the IgG Fc elbow region



Fc fragment	Realtive FcRn affintiy (%)	Half life (T1/2β)
WT	100	62.2±6.0
I253A	21.6±3.0	25.3± 3.8
H310A	7.2±4.8	19.2 ± 2.2
H435A	7.5±0.7	21.7 ± 1.5

Summery II

- Determination of biological half-life: degradation by proteases, target binding to cell bound receptors (antigen sink effect) and renal clearence threshold (MW).

-FcRn binds IgG and albumin in a strictly pH dependent manner simultaneously.

- FcRn recycles IgG and albumin via an efficient recycling pathway (endothelial and hematopoietic cells).
- Explains why IgG and albumin are the only molecules in the blood circulation that have a unique half-life of impressively 20 days.

- Mutation of amino acid residues within the constant Fc region attenuates FcRn binding and consequently biological half-life.

Implications for therapy

- FcRn mediates transport of IgG across cellular barriers (mucosal tissues, alveolar tissues).

- FcRn extends the half-life of IgG and albumin.

Is it possible to use this knowledge to improve therapy?

Intense field of research!

Improving the pharmakokinetics of drugs

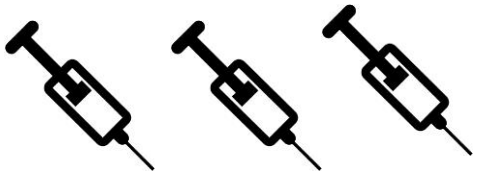
Extending serum half-life

Short-lived biological and chemical drugs

1. A major challenge for the therapeutic use of many drugs is their short lifespan.

2. Removed very rapid from the body (minutes, hours, few days).

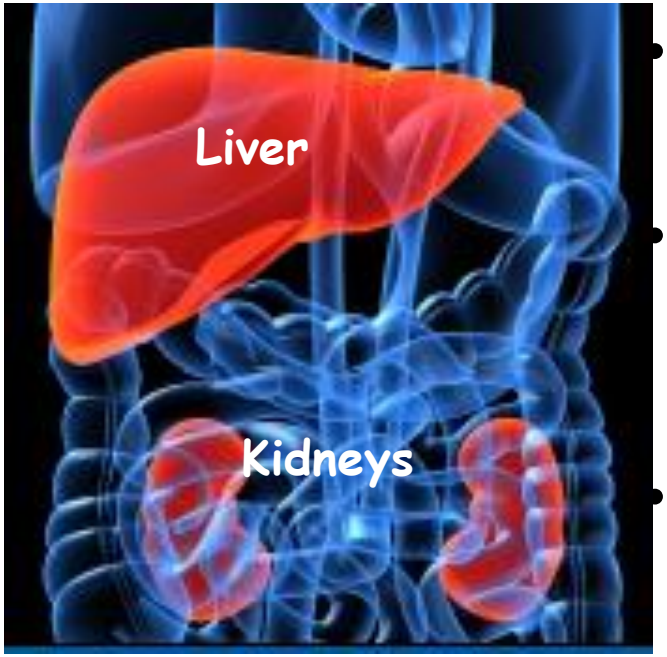
3. Limits their therapeutic efficacy.



4. Expensive treatment, large doses required, burden for the patient.

5. Many promising drug candidates will never reach the marked due to these obstacles!

Why are they eliminated from the body?



- The drugs are small.
- The drugs are removed via the kidneys, excreted in to the urine.
- The drugs are quickly broken down/ metabolized in the liver that receives up to 60 liters of blood each hour.

Extend half-life

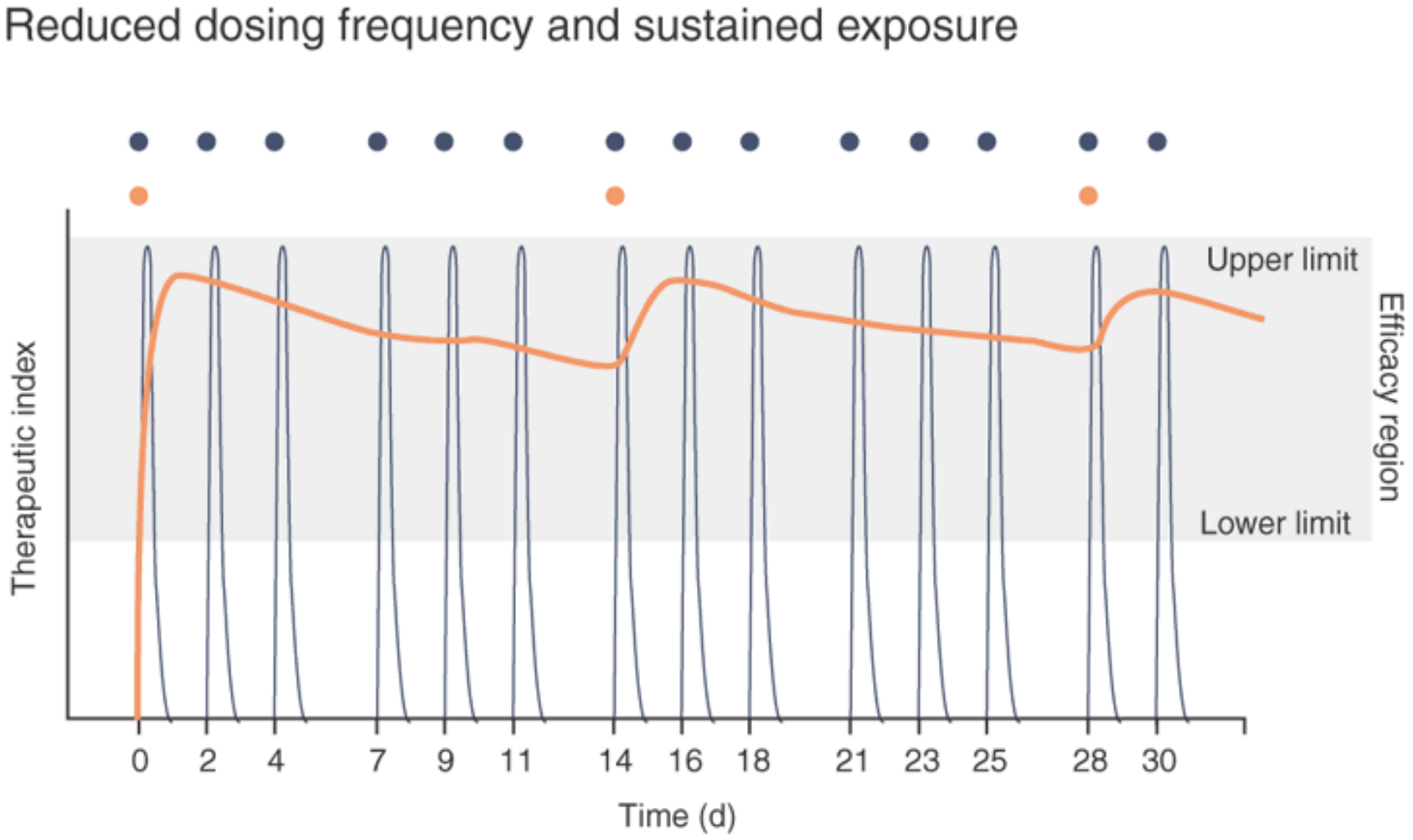
↓

Improve bioavailability

↓

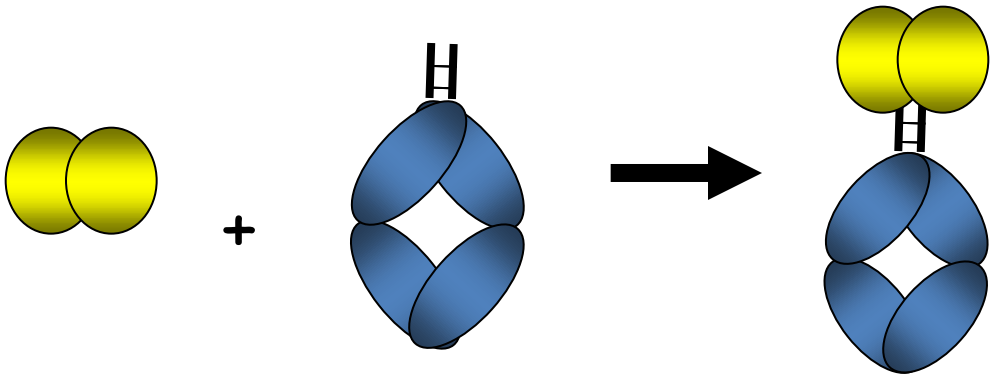
Improve therapeutic outcome

Short half-life versus long serum half-life



IgG Fc fusion technology is currently applied to several classes of therapeutic molecules:

Fc-fused molecules:



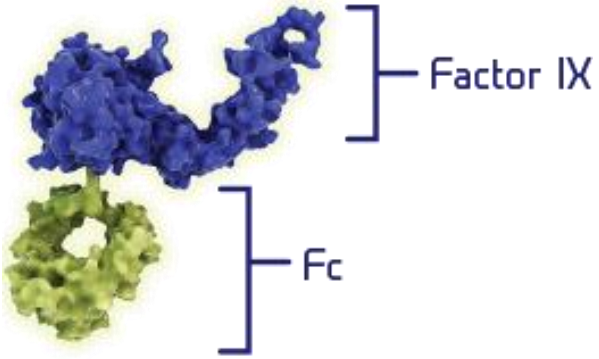
- Incresed half life from 5-50 minutes to several days.

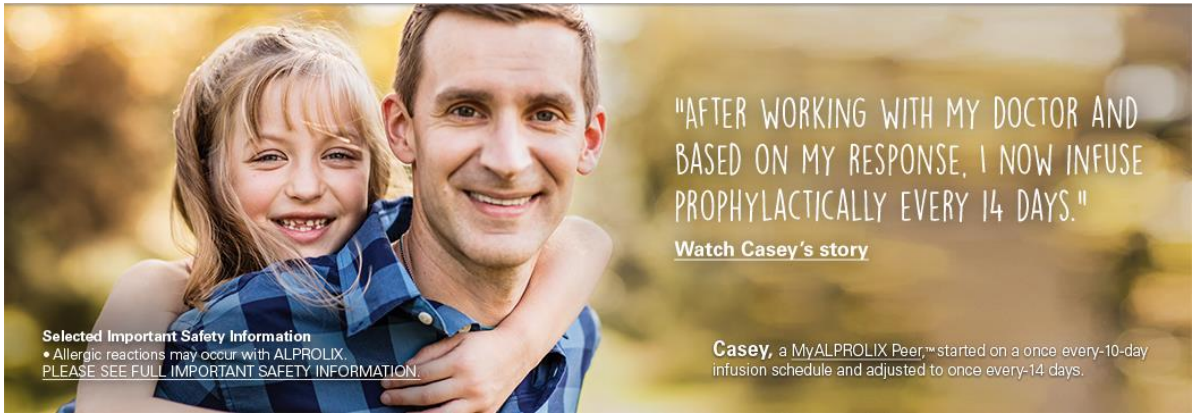
PT	EGF
(TNFα)	MH35BD
ILT3	IP-10
IL-15	PD-L1
Il-4	BP1700
Il-10	hGHR
muIL-17R	VCP
scFv	Tim-3
IL-18bp	BR3
B7.1	CD99
Epo	TNFR
FSH	IL2
CD40	CEA
OX40L	MOG
TrkB-Fc	CD22
ADAMTS	GLP-1
IFNβ	FIX
LIF05	FvIII
CTLA	ATR
GPV1…..	

Jazayeri and Carroll. Fc-based cytokines : prospects for engineering superior therapeutics. BioDrugs. 2008;22(1):11-26. Review.

Factor IX-Fc (ALPROLIX)

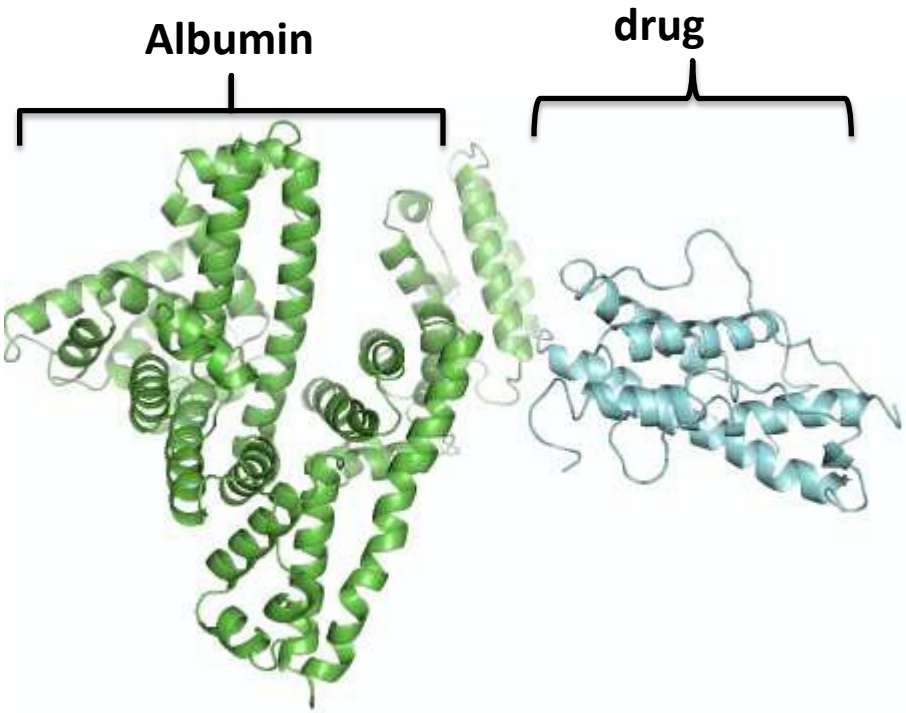
- Approved in 2014 by the U.S. Food and Drug Administration for treatment of hemophilia B.





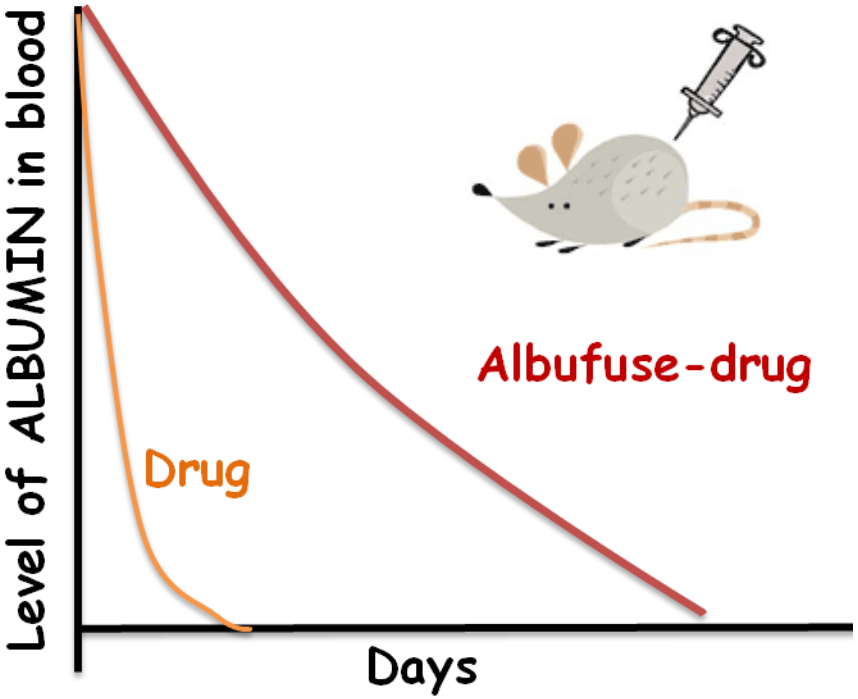
The Veltis technology

Genetic fusion of a drug of interest to albumin



novozymes
Rethink Tomorrow

Albumedix

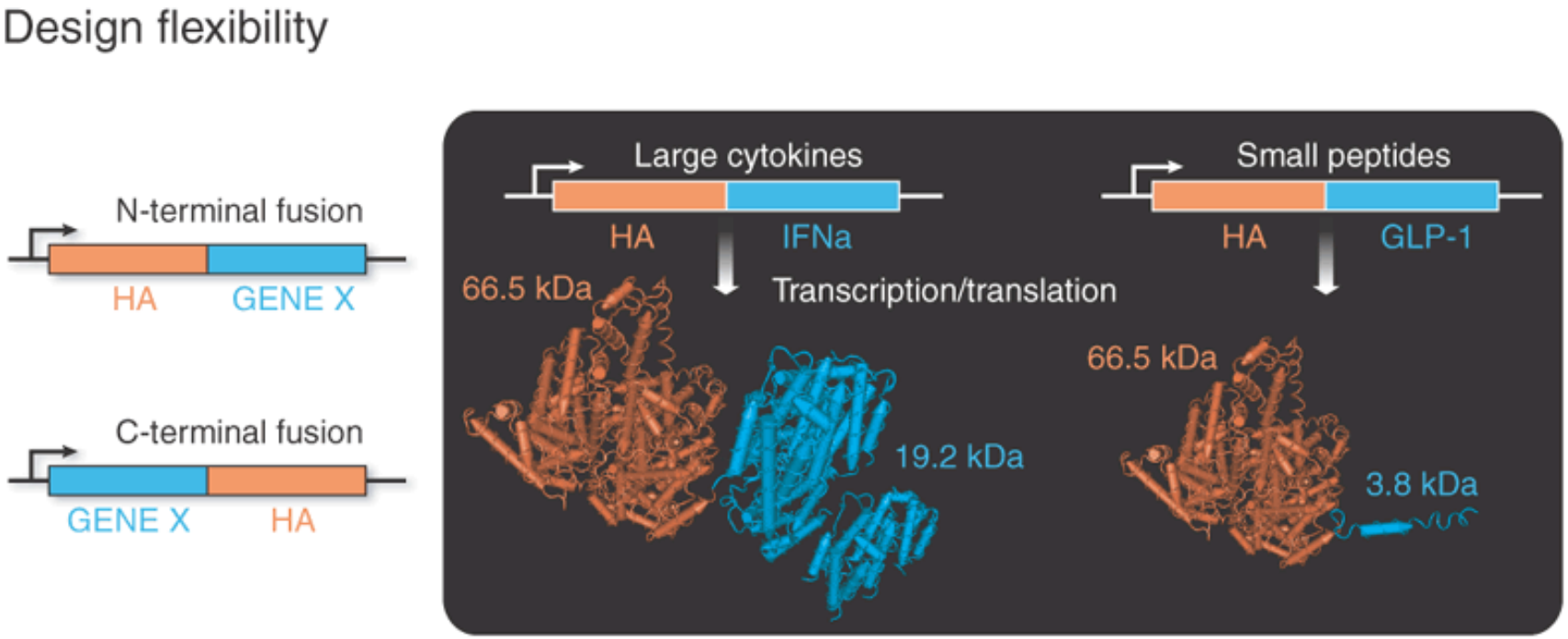


Fusion to albumin extends the lifespan of drugs, improves their bioavailability and therapeutic outcome.

Example of the albumin genetic fusion technology:

- **Avoid IgG Fc mediated side effects.**

- **Human albumin fusion platform: Albufuse™ technology** (Novozymes).



Subramanian et al. Albinterferon alpha-2b: a genetic fusion protein for the treatment of chronic hepatitis C. Nat Biotechnol. 2007 Dec;25(12):1411-9. Review.

Half-life of INF-α in humans:

INF-α variant	T1/2β (h)	Adm.
rINF-α (FDA approved)	4-7.2	3 x week
Alb-INF-α (phase III)	134-153	2-4 week intervals

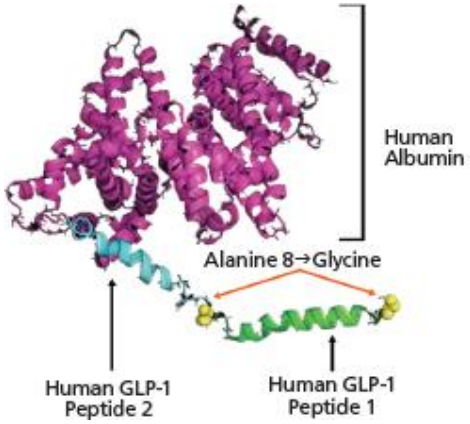
25 fold increased half-life as a consequence of fusion to albumin.

Large effects on treatment regimes!!

The use of IgG Fc and albumin as carriers of drugs

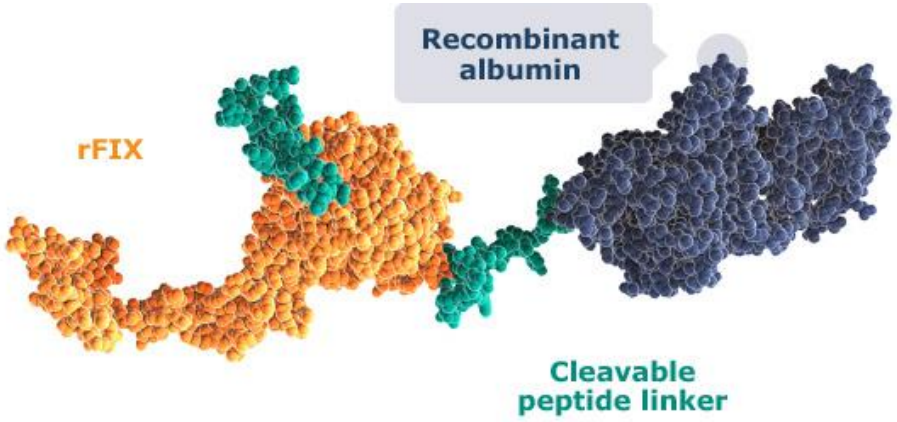
Subramanian et al. Albinterferon alpha-2b: a genetic fusion protein for the treatment of chronic hepatitis C. Nat Biotechnol. 2007 Dec;25(12):1411-9. Review.

Tanzeum/Eperzan - an albumin fusion of GLP-1 for the treatment of type 2 diabetes



Approved 2014.

IDELVION - an albumin fusion to Factor IX for the treatment of hemophilia



Approved 2016.

Extending serum half-life of monoclonal IgG antibodies

Intense interest in design of novel engineered IgGs and albumin with improved serum half-life

IgG and IgG Fc fusions are the fastest growing classes of biopharmaceuticals!

Table 3 The ten top-selling biopharmaceutical products in 2009

Product	Sales value ($ billions)	Company
Enbrel (etanercept)	6.58	Amgen, Wyeth, Takeda Pharmaceuticals
Remicade (infliximab)	5.93	Centocor (Johnson & Johnson), Schering-Plough, Mitsubishi Tanabe Pharma
Avastin (bevacizumab)	5.77	Genentech, Roche, Chugai
Rituxan/MabThera (rituximab)	5.65	Genentech, Biogen-IDEC, Roche
Humira (adalimumab)	5.48	Abbott, Eisai
Epogen/Procrit/Eprex/ESPO (epoetin alfa)	5.03	Amgen, Ortho, Janssen-Cilag, Kyowa Hakko Kirin
Herceptin (trastuzumab)	4.89	Genentech, Chugai, Roche
Lantus (insulin glargine)	4.18	Sanofi-aventis
Neulasta (pegfilgrastim)	3.35	Amgen
Aranesp/Nespo (darbepoetin alfa)	2.65	Amgen, Kyowa Hakko Kirin

Source: LaMerie Business Intelligence, Barcelona

Walsh, Nature Biotech, 2010

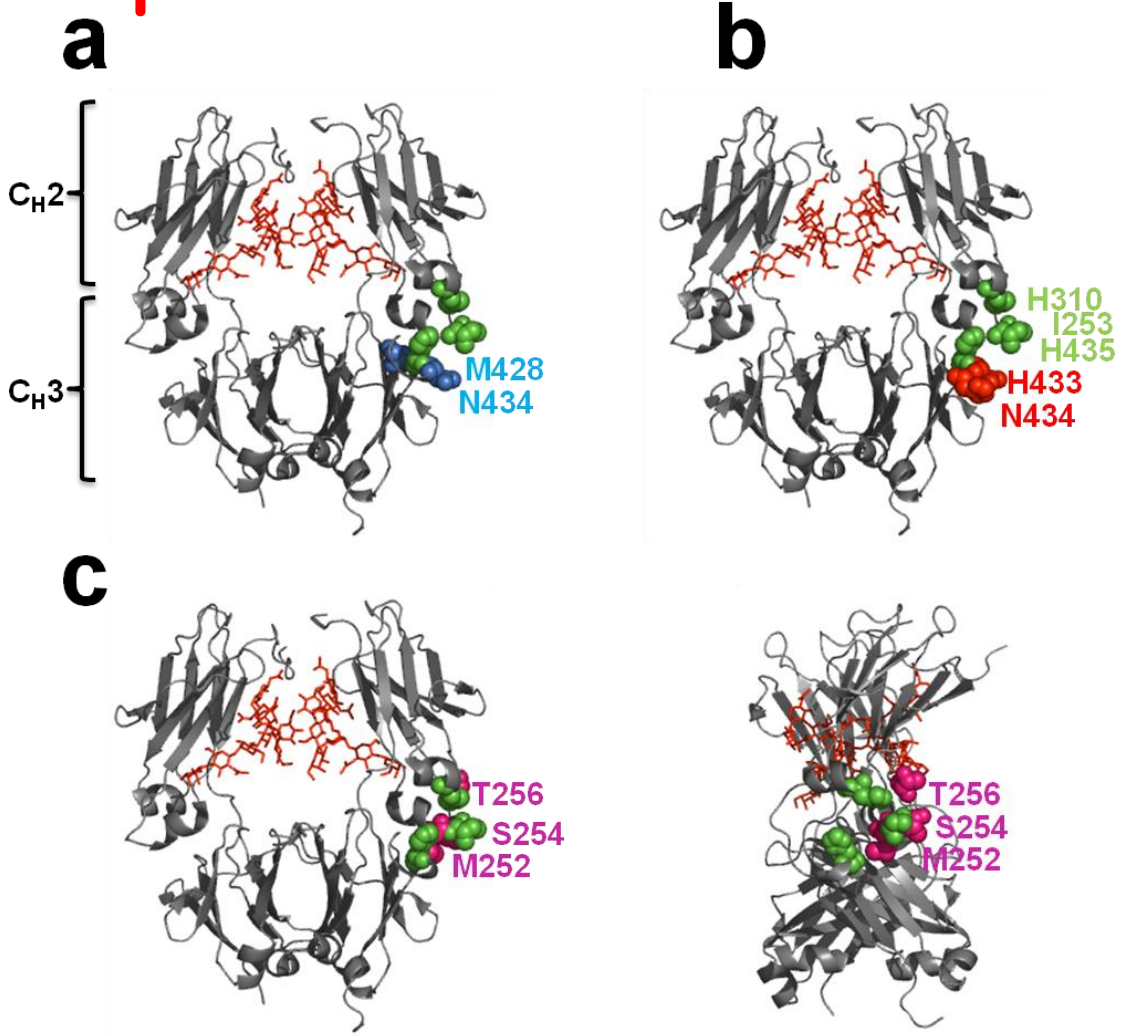
Antibodies are blockbusters

- **Almost 40 antibodies are approved for clinical use.**
- **As of mid-November 2015, 53 novel antibody therapeutics were in Phase III clinical studies.**
- **~210 novel antibody therapeutics are in Phase I or II.**

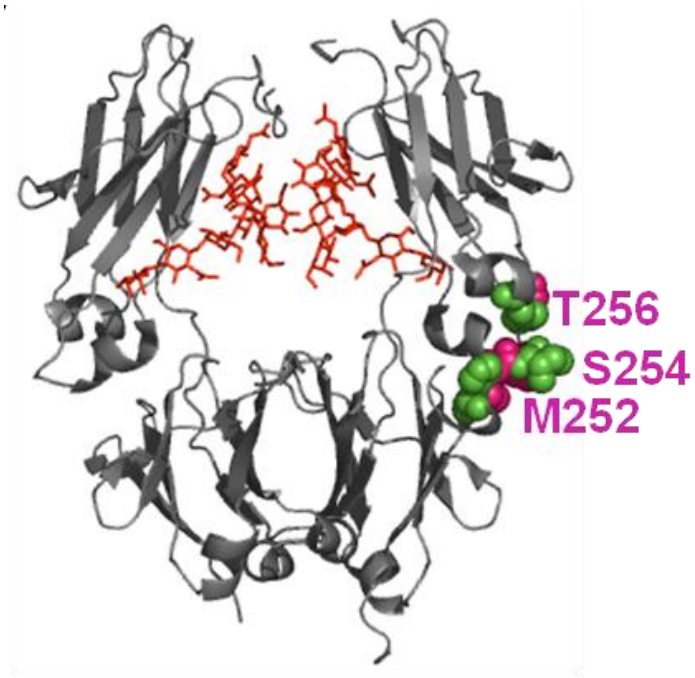
Is it possible to improve serum half-life of IgG beyond that of natural existing IgG antibodies?

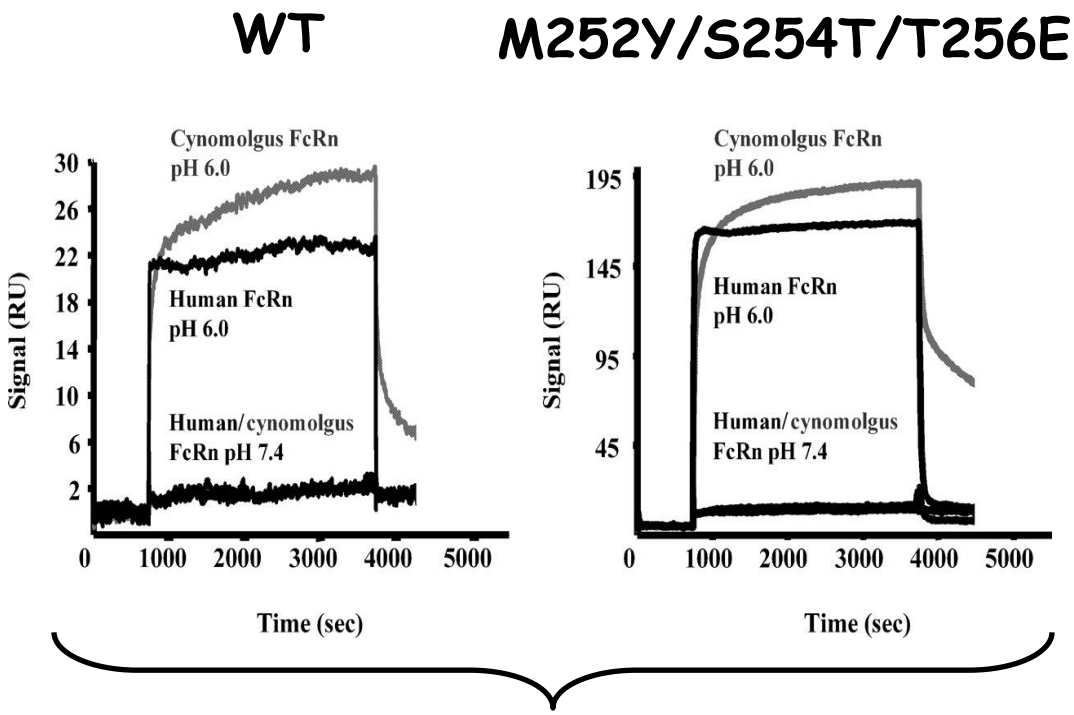
Modulation of FcRn binding by site-directed mutagenesis

Challenge: Improve binding affinity at pH 6.0 with retained pH dependence!



A triple mutant with increased binding affinity FcRn at pH 6.0 with retained pH dependence:



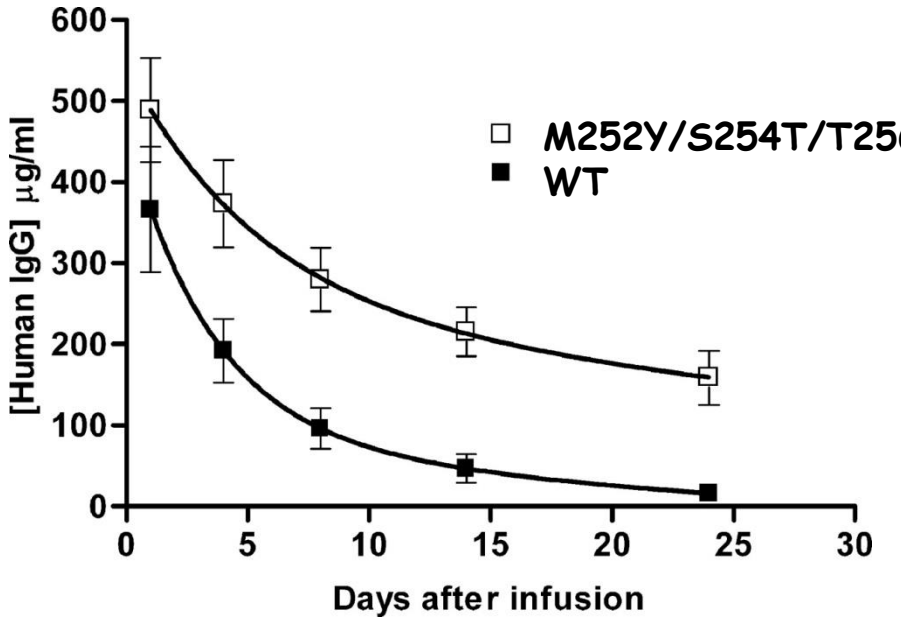


→ **Increased binding affinity at pH 6.0 (~10 fold), retained pH dependence.**

Dall Acqua et al. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). J Biol Chem. 2006 Aug 18;281(33):23514-24. Epub 2006 Jun 21.

Example of increased binding affinity to FcRn pH 6.0 with retained pH dependence:

Clearance curves of the IgG variants in monkeys:



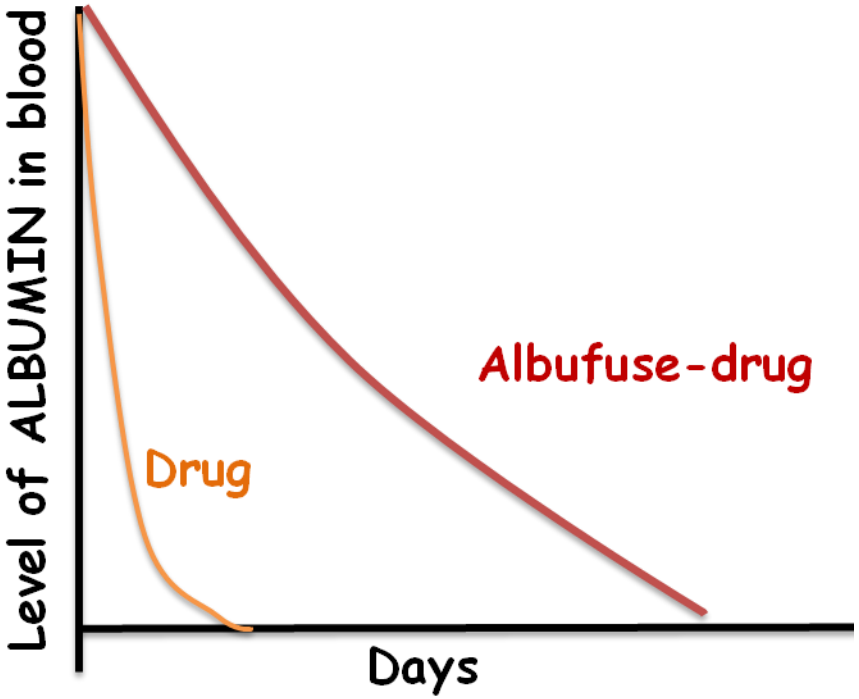
Half-life:

WT	5.9 d
Mutant	21.2 d

Increased binding to FcRn at pH 6.0, retained pH dependence gives incresed half-life.

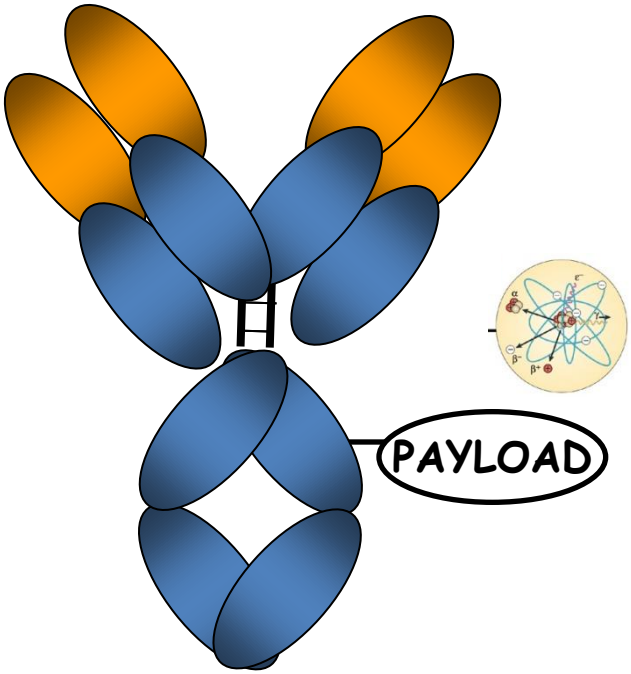
Dall Acqua et al. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). J Biol Chem. 2006 Aug 18;281(33):23514-24.

A similar strategy for albumin?



Can a decrease in IgG half-life have therapeutic implications?

- IgG conjugates (Immunoconjugates) used to deliver toxic principles (radioactive particles, toxins etc) to cancer.



several drawbacks:

1. Unfavorable normal-tissue toxicity (bone marrow, kidney and liver).

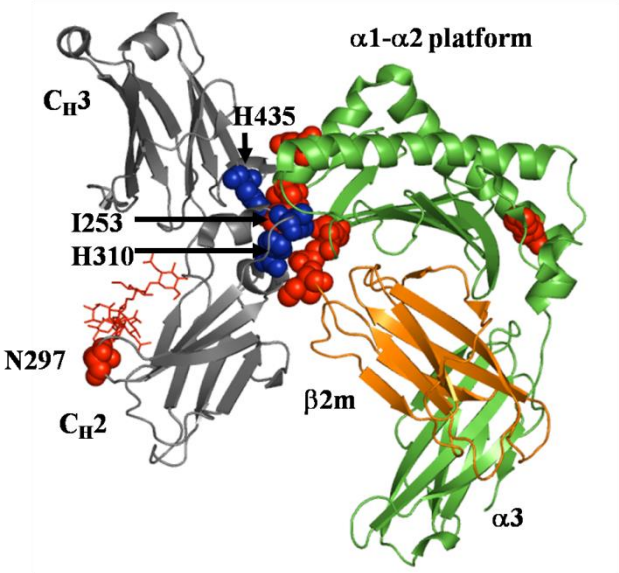
2. Long half-life slows clearence from the body (FcRn).

3. Limits the dosing and treatment regimes of current immunoconjugates in the clinics.

Ricart and Tolcher. Technology insight: cytotoxic drug immunoconjugates for cancer therapy. Nat Clin Pract Oncol. 2007 Apr;4(4):245-55. Review

Modulation of half-life as a function of FcRn binding

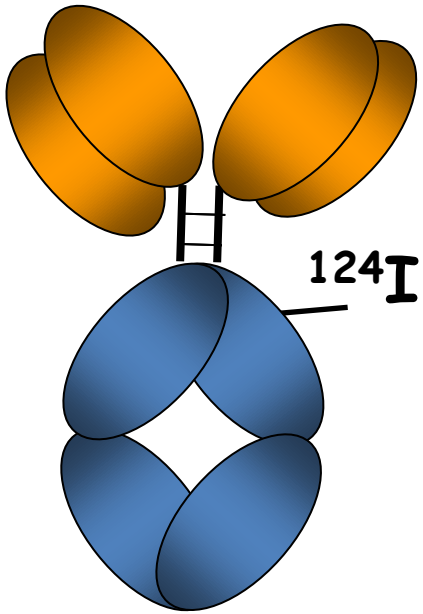
Mutation of amino acid residues in the Fc elbow region



Fc fragment	Realtive FcRn affintiy (%)	Half life (T1/2β)
WT	100	62.2±6.0
I253A	21.6±3.0	25.3± 3.8
H310A	7.2±4.8	19.2 ± 2.2
H435A	7.5±0.7	21.7 ± 1.5

Example of a therapeutic benefit of reduced half-life as a consequence of reduced binding to FcRn:

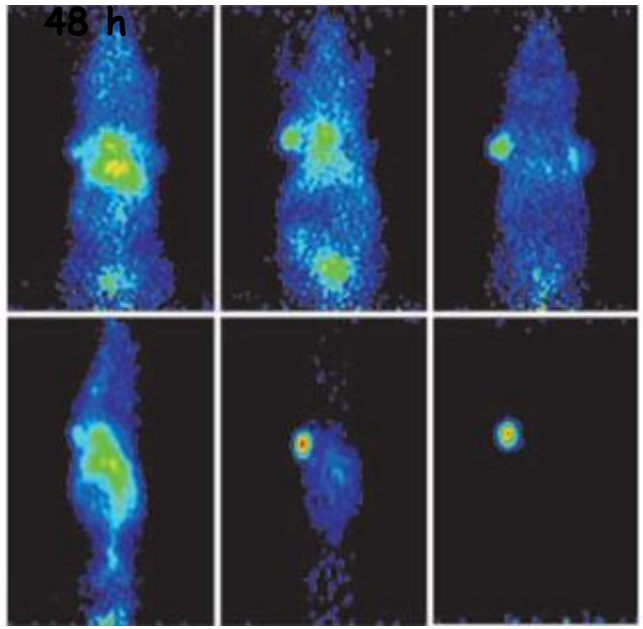
Immunoconjugate:
^{124}I-labeled anti-CEA scFv-Fc



WT → **Binds FcRn!**

H310A/H435A → **No binding to FcRn!**

Imaging of CEA postive tumor in mice using the ^{124}I-labeled anti-CEA scFv-Fc fragments



→ **The half-life of Immunoconjugates can be modulated as a function of FcRn binding affinity.**

Wu and Senter. Arming antibodies: prospects and challenges for immunoconjugates. Nat Biotechnol. 2005 Sep;23(9):1137-46. Review.

Mother

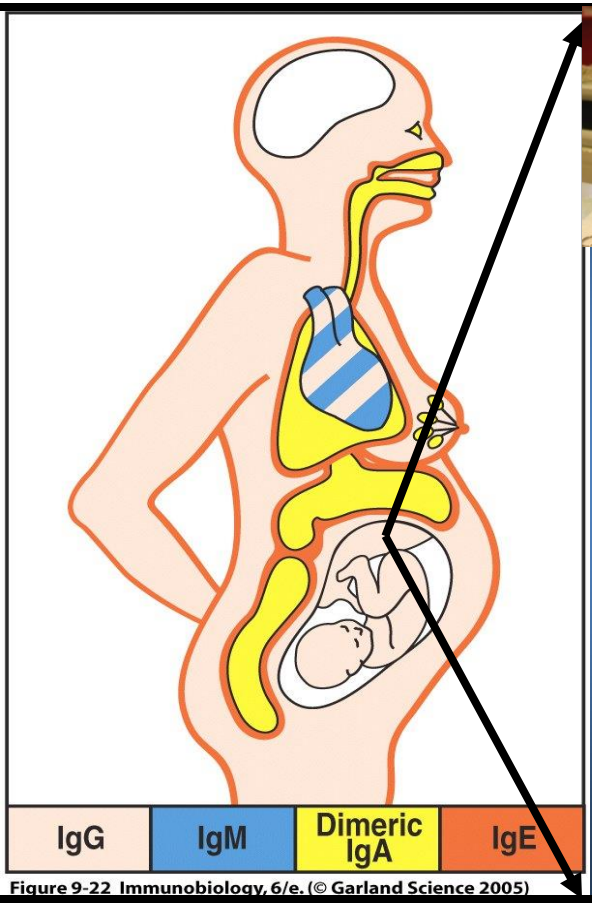
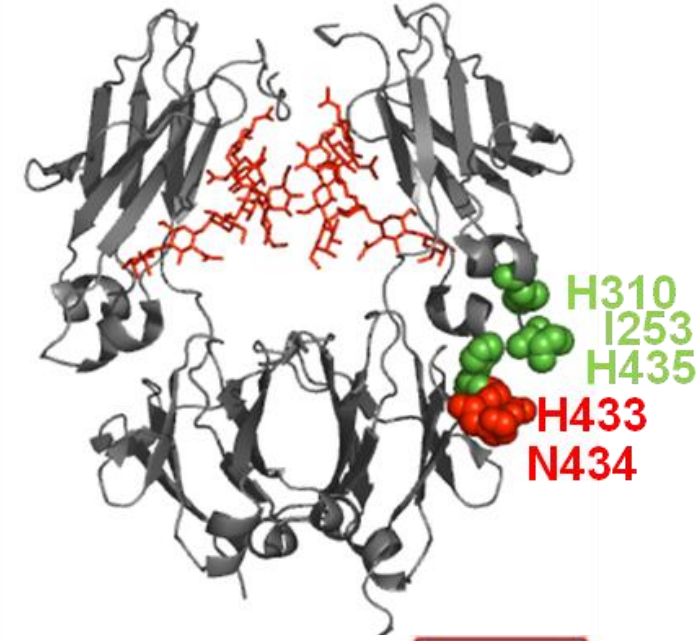


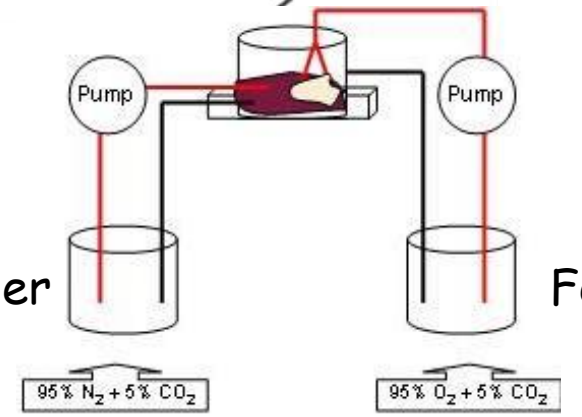
Figure 9-22 Immunobiology, 6/e. (© Garland Science 2005)

- FcRn mediates transplacental transport of IgG from mother to fetus): <u>passive immunization</u>.

Fetus

Transplacental delivery: FcRn mediated *In utero* therapy?

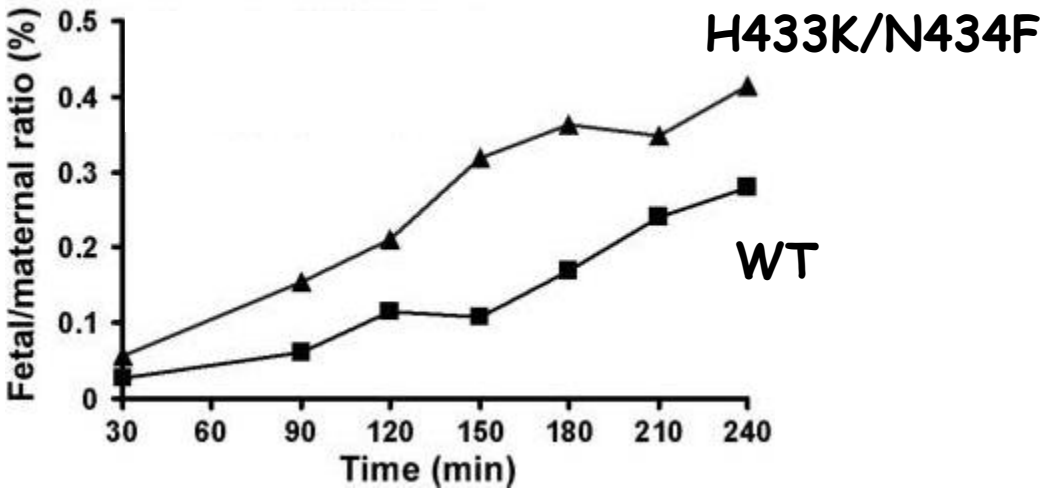




Mother

Fetus

	WT (nM)	H433K/N434F (nM)
hFcRn (pH 6.0)	528	34
hFcRn (pH7.4)	ND	ND



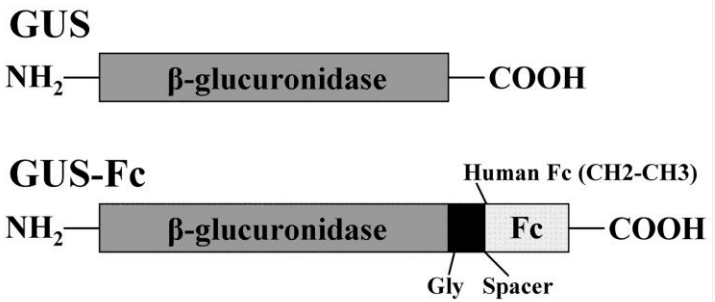
Optimized transplacental efficency as a function of altered FcRn binding affinity.

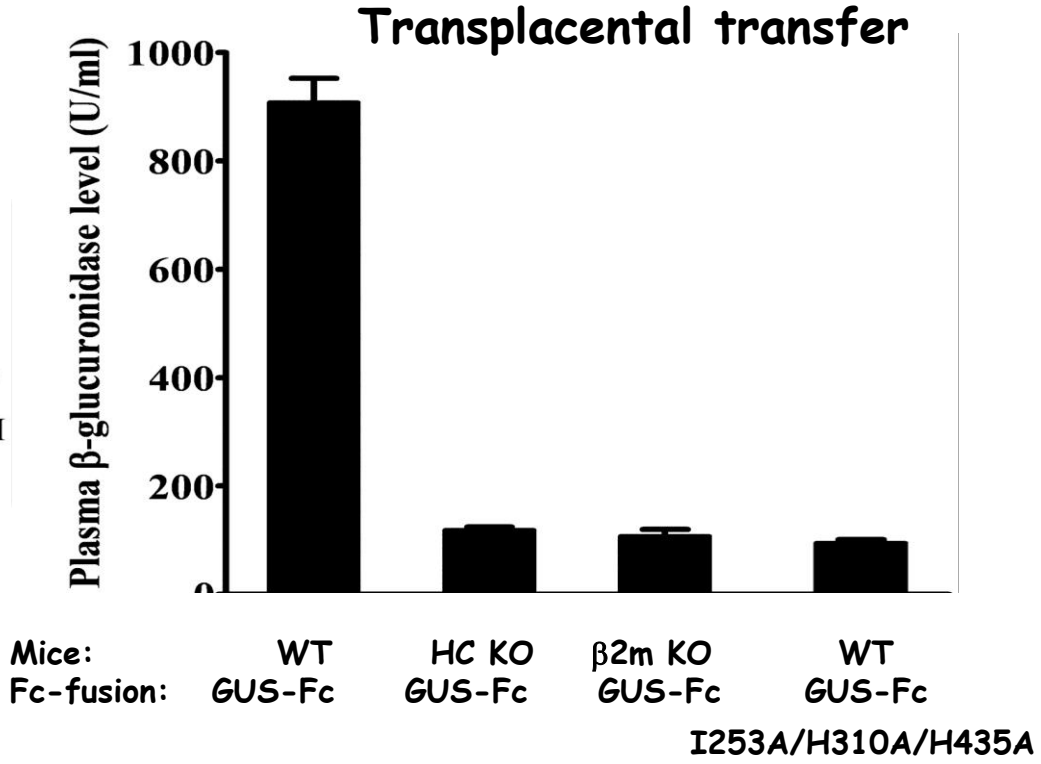
Vaccaro et al. Divergent activities of an engineered antibody in murine and human systems have implications for therapeutic antibodies. Proc Natl Acad Sci U S A. 2006 Dec 5;103(49):18709-14.

Transplacental delivery of Fc-fused drugs:

Combine "enzyme-replacement therapy (ERT)" with FcRn mediated transplacental transport:

β-glucurosidase-Fc fusion:





→ ***In utero*** **FcRn mediated transport of a Fc-fused therapeutic.**

Grubb et al. Infused Fc-tagged beta-glucuronidase crosses the placenta and produces clearance of storage in utero in mucopolysaccharidosis VII mice.Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8375-80.

Summery III

- FcRn is a versatile receptor with several important functions that can be utilized therapeutically.
- Extend the pharmacokinetics of therapeutics by IgG Fc or albumin fusion technologies (carrier).
- Extend the pharmacokinetics of therapeutic monoclonal IgGs by engineering the FcRn-IgG interaction.
- Attenuating the FcRn-IgG interaction to tailor the pharmacokinetics of immunoconjugates.
- FcRn mediated transplacental delivery of IgG or Fc fusion therapeutics.

Student buzz

1. What is the consequence of blocking the IgG binding site on FcRn (anti-FcRn Ab, anti-FcRn peptide)?

2. Has the effect of FcRn blocking relevance for therapy?

3. What will happen with an engineered IgG molecule that binds strongly to FcRn in an pH independent manner?

4. Has the use of such IgGs any therapeutic utility?